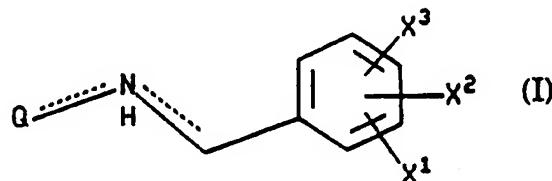




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(54) Title: FLUOROALKOXYBENZYLAMINO DERIVATIVES OF NITROGEN CONTAINING HETEROCYCLES

**BEST AVAILABLE COPY****(57) Abstract**

The present invention relates to novel fluoroalkoxybenzylamino derivatives of nitrogen containing heterocyclic compounds, and specifically, to compounds of formula (I) wherein Q, X¹, X² and X³ are as defined below. These novel compounds are useful in the treatment of inflammatory and central nervous system disorders, as well as other disorders.

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5 FLUOROALKOXYBENZYLAMINO DERIVATIVES OF NITROGEN CONTAINING HETEROCYCLES

Background of the Invention

The present invention relates to novel fluoroalkoxybenzylamino derivatives of nitrogen containing heterocycles, pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment and prevention of inflammatory and central nervous system disorders, as well as several other disorders. The pharmaceutically active compounds of this invention are substance P receptor antagonists. This invention also relates to novel intermediates used in the synthesis of such substance P receptor antagonists.

Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being named because of their prompt stimulatory action on smooth muscle tissue. More specifically, substance P is a pharmacologically active neuropeptide that is produced in mammals (having originally been isolated from gut) and possesses a characteristic amino acid sequence that is illustrated by D. F. Veber *et al.* in U.S. Patent No. 4,680,283. The wide involvement of substance P and other tachykinins in the pathophysiology of numerous diseases has been amply demonstrated in the art. For instance, substance P has recently been shown to be involved in the transmission of pain or migraine (see B.E.B. Sandberg *et al.*, Journal of Medicinal Chemistry, 25, 1009 (1982)), as well as in central nervous system disorders such as anxiety and schizophrenia, in respiratory and inflammatory diseases such as asthma and rheumatoid arthritis, respectively, in rheumatic diseases such as fibrositis, and in gastrointestinal disorders and diseases of the GI tract such as ulcerative colitis and Crohn's disease, etc. (see D. Regoli in "Trends in Cluster Headache," edited by F. Sicuteri *et al.*, Elsevier Scientific Publishers, Amsterdam, pp. 85-95 (1987)).

40 In the recent past, some attempts have been made to provide antagonists for substance P and other tachykinin

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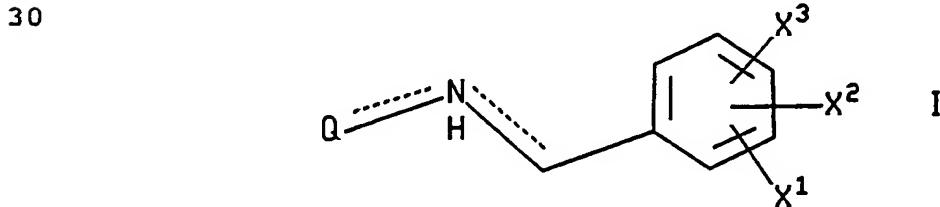
peptides in order to more effectively treat the various disorders and diseases listed above. The few such antagonists thus far described are generally peptide-like in nature and are therefore too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, being far more stable from a metabolic point of view than the agents referred to above.

Quinuclidine derivatives and related compounds that exhibit activity as substance P receptor antagonists are referred to in PCT Patent Application PCT/US 89/05338, filed November 20, 1989 and United States Patent Application Serial No. 557,442, filed July 23, 1990, both of which are assigned in common with the present application. Similar compounds are referred to in PCT patent applications PCT/US 91/02853 and PCT/US 91/03369, filed on April 25, 1991 and May 15, 1991, respectively. These applications are also assigned in common with the present application.

Piperidine derivatives and related heterocyclic nitrogen containing compounds that are useful as substance P antagonists are referred to in United States Patent Application Serial No. 619,361, filed November 28, 1990 and United States Patent Application Serial No. 590,423, filed September 28, 1990, both of which are assigned in common with the present application.

Summary of the Invention

The present invention relates to compounds of the formula



35

wherein X¹ is hydrogen, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms or (C₁-C₁₀) alkyl

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optionally substituted with from one to three fluorine atoms;

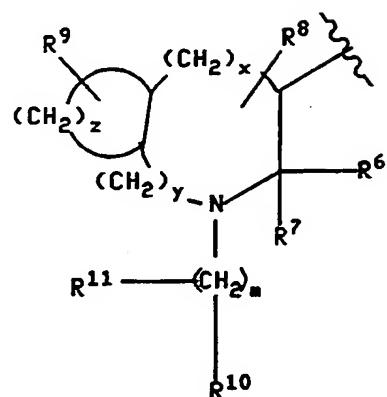
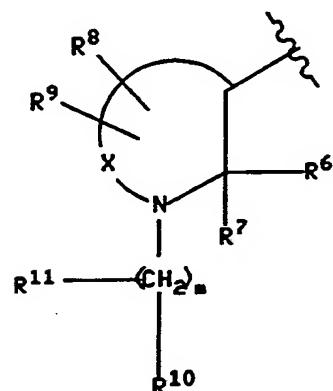
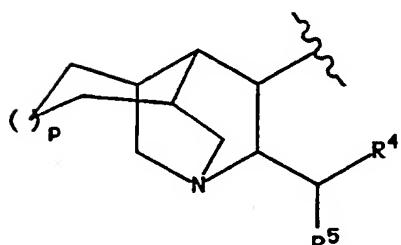
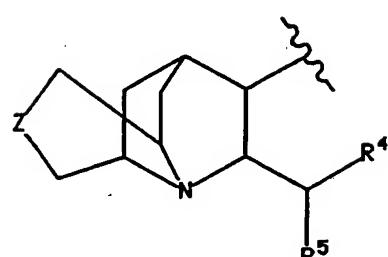
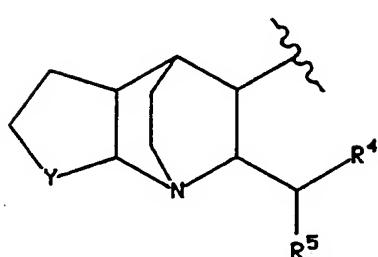
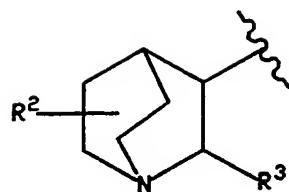
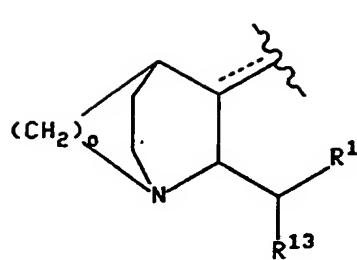
X² and X³ are independently selected from hydrogen, halo, nitro, (C₁-C₁₀) alkyl optionally substituted with from 5 one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C₁-C₆)-

10 alkylamino, di-(C₁-C₆)alkylamino, -C^O=NH-(C₁-C₆)alkyl,

15 (C₁-C₆) alkyl-C^O=NH-(C₁-C₆) alkyl, hydroxy(C₁-C₄)alkyl,

(C₁-C₄)alkoxy(C₁-C₄)alkyl, -NHCH^O and -NHC^O-(C₁-C₆) alkyl; and
20 Q is a group of the formula

-4-



-5-

wherein R¹ is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C₁-C₃) alkoxy-carbonyl;

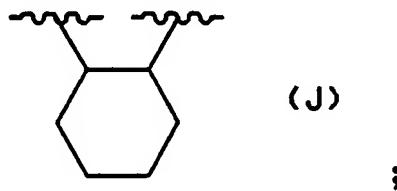
R¹³ is selected from (C₃-C₄) branched alkyl, (C₅-C₆) branched alkenyl, (C₅-C₇) cycloalkyl, and the radicals named in the definition of R¹;

R² is hydrogen or (C₁-C₆) alkyl;

R³ is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R³ may optionally be substituted with from one to three substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms;

Y is (CH₂)_l wherein l is an integer from one to three, or Y is a group of the formula

20



25

Z is oxygen, sulfur, amino, (C₁-C₃)alkylamino or (CH₂)_n, wherein n is zero, one or two;

o is two or three;

30 p is zero or one;

R⁴ is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, (C₁-C₃) alkoxy-carbonyl and benzyloxycarbonyl;

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R⁵ is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms;

each of the two dashed lines in formula I and the dashed line in formula II represent an optional double bond that may optionally exist when Q is a group of the formula II;

X is (CH₂)_q wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said (CH₂)_q may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said (CH₂)_q may optionally be substituted with R⁸, and wherein any one of the carbon atoms of said (CH₂)_q may optionally be substituted with R⁹;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of (CH₂)_m may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said (CH₂)_m may optionally be substituted with R¹¹;

R⁶ is a radical selected from hydrogen, (C₁-C₆) straight or branched alkyl, (C₃-C₇) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C₂-C₆) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C₂-C₆) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C₁-C₆) alkyl, (C₁-C₆) alkoxy-(C₁-C₆) alkyl,

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O O
 (C_1-C_6) -alkylamino, (C_1-C_6) alkyl-O-C-, (C_1-C_6) alkyl-O-C-

5 O O
 (C_1-C_6) alkyl, (C_1-C_6) alkyl-C-O-, (C_1-C_6) alkyl-C-

10 O O
 (C_1-C_6) alkyl-O-, (C_1-C_6) alkyl-C-, (C_1-C_6) alkyl-C-

15 O
 (C_1-C_6) alkyl-, di- (C_1-C_6) alkylamino, -CNH-(C_1-C_6) alkyl, (C_1-C_6) -

O O O
alkyl-C-NH-(C_1-C_6) alkyl, -NHCH and -NHC-(C_1-C_6) alkyl; and
20 wherein one of the phenyl moieties of said benzhydryl may
optionally be replaced by naphthyl, thienyl, furyl or
pyridyl;

R⁷ is hydrogen, phenyl or (C_1-C_6) alkyl;
or R⁶ and R⁷, together with the carbon to which they are
25 attached, form a saturated carbocyclic ring having from 3 to
7 carbon atoms wherein one of said carbon atoms may
optionally be replaced by oxygen, nitrogen or sulfur;

R⁸ and R⁹ are each independently selected from hydrogen,
hydroxy, halo, amino, oxo (=O), nitrile, hydroxy-(C_1-
30 C_6) alkyl, (C_1-C_6) alkoxy-(C_1-C_6) alkyl, (C_1-C_6) alkylamino,
di- (C_1-C_6) alkylamino, (C_1-C_6) alkoxy,

O O
35 (C_1-C_6) alkyl-O-C-, (C_1-C_6) alkyl-O-C-(C_1-C_6) alkyl,
O O
 (C_1-C_6) alkyl-C-O-, (C_1-C_6) alkyl-C-(C_1-C_6) alkyl-O-,

40 O O
 (C_1-C_6) alkyl-C-, (C_1-C_6) alkyl-C-(C_1-C_6) alkyl-, and the radicals
set forth in the definition of R⁶;

45 R¹⁰ is NHCR¹², NHCH₂R¹², NHSO₂R¹² or one of the radicals set
forth in any of the definitions of R⁶, R⁸ and R⁹;

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R¹¹ is oximino (=NOH) or one of the radicals set forth in any of the definitions of R⁶, R⁸ and R⁹; and

R¹² is (C₁-C₆)alkyl, hydrogen, phenyl(C₁-C₆)alkyl or phenyl optionally substituted with (C₁-C₆) alkyl; and

- 5 with the proviso that (a) when m is 0, R¹¹ is absent, (b) neither R⁸, R⁹, R¹⁰ nor R¹¹ can form, together with the carbon to which it is attached, a ring with R⁷, (c) when Q is a group of the formula VIII, R⁸ and R⁹ cannot be attached to the same carbon atom, (d) when R⁸ and R⁹ are attached to the
10 same carbon atom, then either each of R⁸ and R⁹ is independently selected from hydrogen, fluoro, (C₁-C₆) alkyl, hydroxy-(C₁-C₆)alkyl and (C₁-C₆)alkoxy-(C₁-C₆)alkyl, or R⁸ and R⁹, together with the carbon to which they are attached, form a (C₃-C₆) saturated carbocyclic ring that forms a spiro
15 compound with the nitrogen-containing ring to which they are attached, (e) the nitrogen of formula I can not be double bonded to both Q and the substituted benzyl group to which it is attached, (f) when Q is a group of the formula VII and q is 2 and either R⁸ or R⁹ is 5-hydroxy-(C₁-C₆)alkyl or
20 5-(C₁-C₆)alkoxy-(C₁-C₆)alkyl, then the other of R⁸ and R⁹ is either 5-(C₁-C₃)alkyl or hydrogen; (g) when Q is a group of the formula VII and q is 2, then neither R⁸ nor R⁹ is 4-hydroxy-(C₁-C₆)alkyl or 4-(C₁-C₆)alkoxy-(C₁-C₆)alkyl, and (h)
25 when neither X¹, X² nor X³ is a fluorinated alkoxy group, at least one of R¹, R³, R⁴, R⁵, R⁶, R⁷ and R¹³ is an aryl group substituted with a fluorinated alkoxy group.

The present invention also relates to the pharmaceutically acceptable acid addition and base salts of compounds of the formula I. The acids which are used to
30 prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate,

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maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

5 The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or
10 combinations thereof.

The term "one or more substituents," as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

Preferred compounds of the formula I are those wherein
15 R¹, R⁴, R⁵ and R⁷ are phenyl, R² is hydrogen, R³ is phenyl optionally substituted with chlorine, fluorine, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms or (C₁-C₆) alkoxy optionally substituted with from one to three fluorine atoms, m is 0 and n is 3 or 4.

20 Specific preferred compounds of the formula I are:

(2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;

(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine;

25 (2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine;

30 (2S,3S)-3(-5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

2-(diphenylmethyl)-N-(2-methoxy-5-trifluoromethoxy-phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-3-[5-chloro-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine;

35 (2S,3S)-3-(5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

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(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-difluoromethoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine;

5 (2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxybenzyl)-aminopiperidine; and

(2S,3S)-2-phenyl-3-(2-trifluoromethoxybenzyl)aminopiperidine.

Other compounds of the formula I are:

10 3-[N-(2-methoxy-5-trifluoromethoxybenzyl)-amino]-5,5-dimethyl-2-phenylpyrrolidine;

3-[N-(2-methoxy-5-trifluoromethoxybenzyl)amino]-4,5-dimethyl-2-phenylpyrrolidine;

15 3-(2-cyclopropoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(2-cyclopropylmethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(2-difluoromethoxy-5-phenylbenzyl)amino-2-phenylpiperidine;

20 3-(5-cyclopropylmethoxy-2-difluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)-piperidine;

25 3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;

2-phenyl-3-(5-n-propyl-2-trifluoromethoxybenzyl)amino-piperidine;

3-(5-isopropyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

30 3-(5-ethyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

3-(5-sec-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

35 3-(5-difluoromethoxy-2-methoxybenzyl)amino-2-phenylpiperidine;

3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpyrrolidine;

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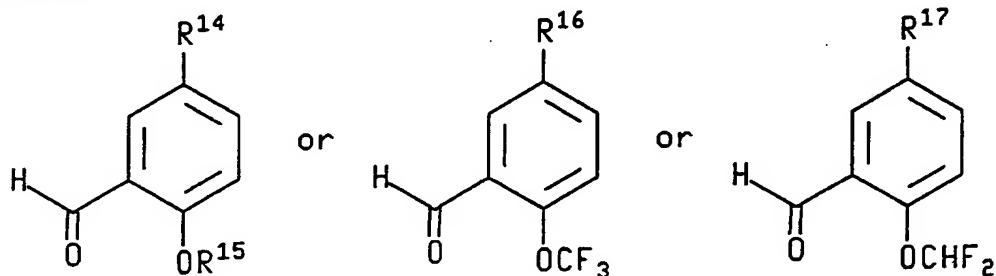
- 3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylhomopiperidine;
- 2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminopyrrolidine;
- 5 2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminohomopiperidine;
- 3-[2,5-bis-(2,2,2-trifluoroethoxy)benzyl]amino-2-phenylpiperidine;
- 2-phenyl-3-(3-trifluoromethoxybenzyl)aminopiperidine;
- 10 2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)-aminopiperidine;
- 1-(5,6-difluorohexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
- 15 1-(6-hydroxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;
- 3-phenyl-4-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-azabicyclo[3.3.0]octane;
- 4-benzhydryl-5-(2-methoxy-5-trifluoromethoxybenzyl)-amino-3-azabicyclo[4.1.0]heptane;
- 20 4-(2-methoxy-5-trifluoromethoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane;
- 2-phenyl-3-(2-methoxy-5-trifluoromethoxybenzyl)-aminoquinuclidine;
- 8-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-9-
- 25 azatricyclo[4.3.1.0^{4,9}]decan-7-amine;
- 9-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-10-azatricyclo[4.4.1.0^{5,10}]undecan-8-amine;
- 9-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-3-thia-10-azatricyclo[4.4.1.0^{5,10}]undecan-8-amine;
- 30 8-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-9-azatricyclo[4.3.1.0^{4,9}]decan-7-amine;
- 5,6-pentamethylene-2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl)aminoquinuclidine;
- 5,6-trimethylene-2-benzhydryl-3-(2-methoxy-5-trifluoro-
- 35 methoxybenzyl)aminoquinuclidine;
- 9-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-3-oxa-10-azatricyclo[4.4.1.0^{5,10}]undecan-3-amine;

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8-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-7-azatricyclo[4.4.1.0^{5,10}]undecan-9-amine; and

2-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-1-azabicyclo[3.2.2]nonan-3-amine.

- 5 The present invention also relates to a compound of the formula



wherein R¹⁴ trifluoromethoxy or difluoromethoxy, R¹⁵ is (C₁-C₄)alkyl, R¹⁶ is difluoromethoxy or (C₁-C₄)alkyl and R¹⁷ is trifluoromethoxy, difluoromethoxy, (C₁-C₄)alkyl or (C₁-C₄)alkoxy.

- 10 The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, gastroesophageal reflux disease, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrosis in a mammal, including a human, comprising an amount of a compound of the formula

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I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of
5 treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, gastroesophageal reflux disease, allergies such as eczema
10 and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such
15 as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to
20 immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in
25 treating or preventing such condition.

The present invention also relates to a pharmaceutical composition for antagonizing the effects of substance P in a mammal, including a human, comprising a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of antagonizing the effects of substance P in a mammal, including a human, comprising administering to said mammal
35 a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

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The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising a substance P antagonizing amount of 5 a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in a mammal, including a 10 human, resulting from an excess of substance P, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical 15 composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, gastroesophageal reflux disease, 20 allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex 25 sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple 30 sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrosis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective 35 in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

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The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, gastroesophageal reflux disease, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as 15 Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to 20 said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of 25 substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or 30 facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a

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pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder.

The compounds of the formula I have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula I, and mixtures thereof.

Formula I above includes compounds identical to those depicted but for the fact that one or more hydrogen or carbon atoms are replaced by radioactive isotopes thereof. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmokinetic studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and in vivo binding studies, while specific applications in the diagnostic area include studies of the substance P receptor in the human brain in in vivo binding in the relevant tissues for inflammation, e.g. immune-type cells or cells that are directly involved in inflammatory bowel disorders and the like. Included among the radiolabelled forms of

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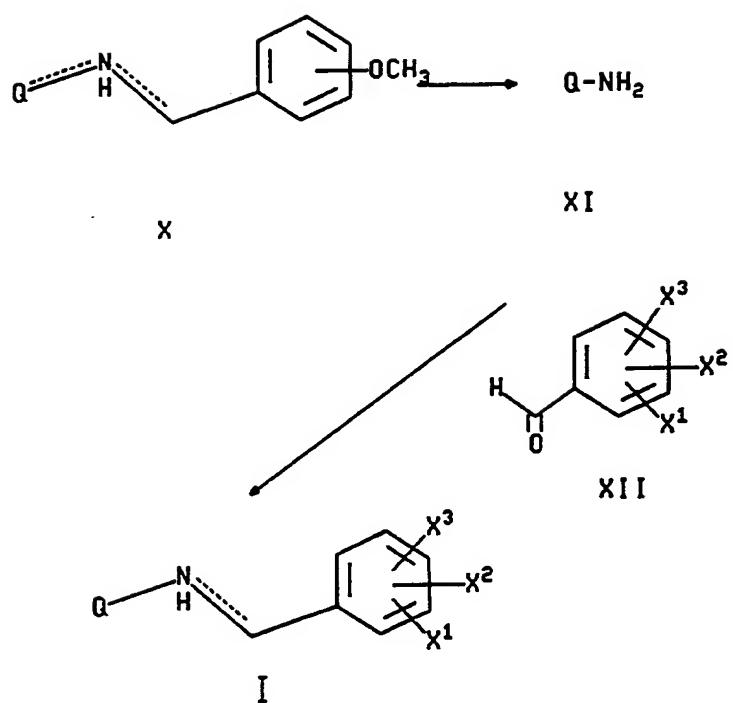
compounds of the formula I are the tritium and C¹⁴ isotopes thereof.

Detailed Description of the Invention

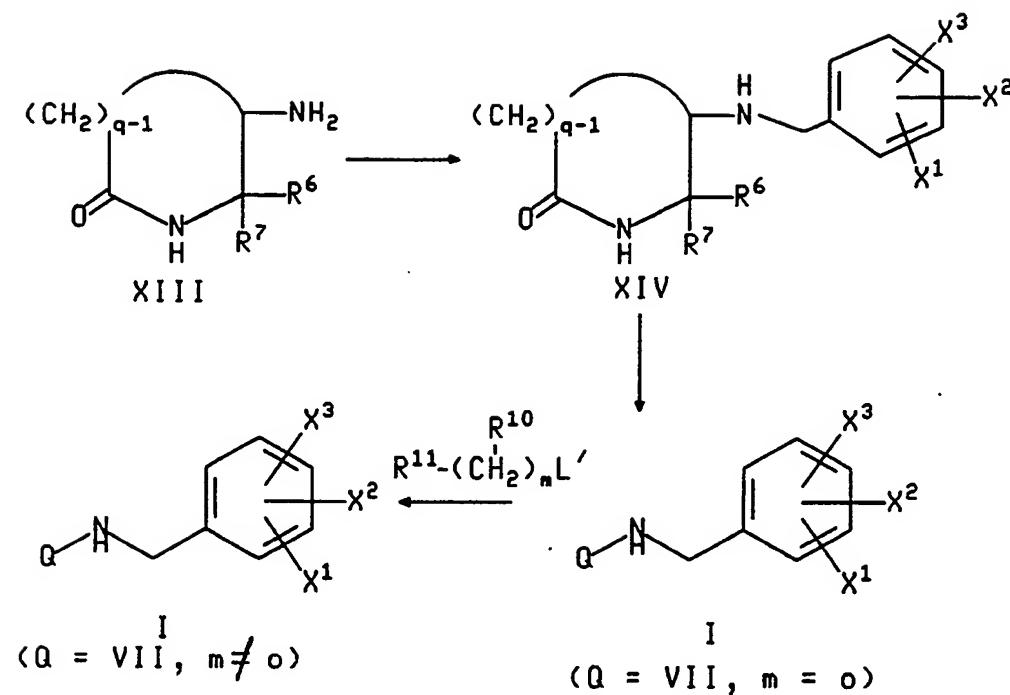
The compounds of the formula I may be prepared as
5 described in the following reaction schemes and discussion.
Unless otherwise indicated, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹,
R¹⁰, R¹¹, R¹², R¹³, X, Z, Q, Y, m, n, o, p, q, x, y, and z in
the reaction schemes and discussion that follow are defined
as above.

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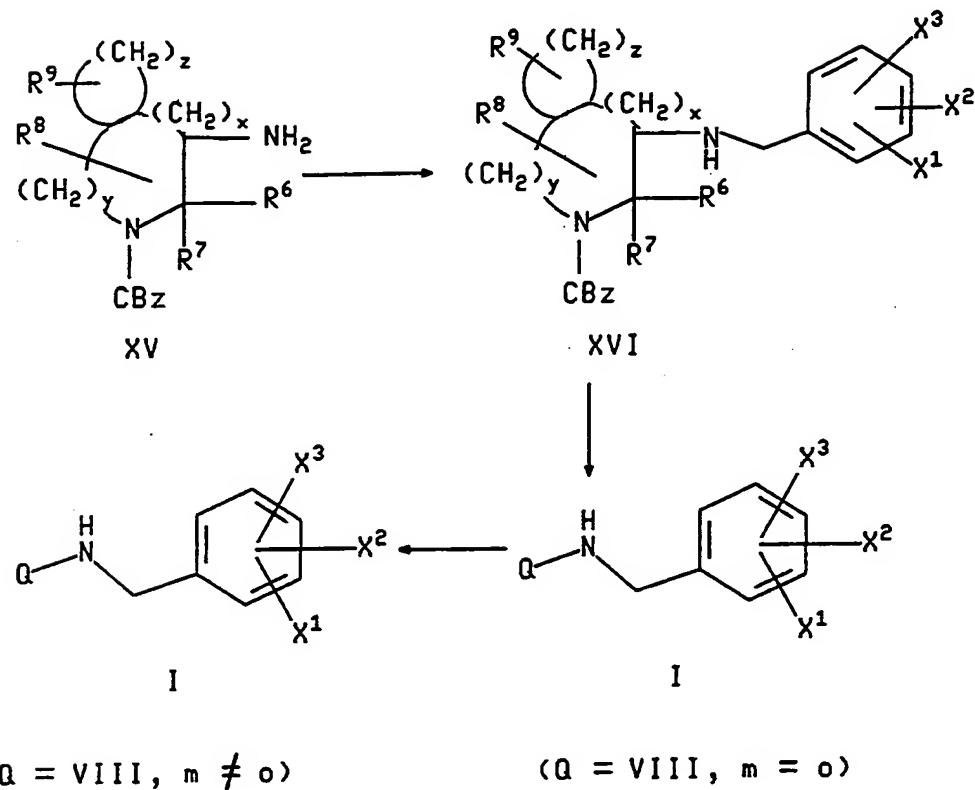
Scheme 1



-19-

Scheme 2

-20-

Scheme 3

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Compounds of the formula I may be prepared by the methods illustrated in schemes 1 and 2.

Referring to scheme 1, compounds of the formula X may be subjected to hydrolytic removal of the methoxybenzyl group using a strong mineral acid such as hydrochloric, hydrobromic or hydroiodic acid, at a temperature from about room temperature to about the reflux temperature of the acid. Preferably, the reaction is conducted in hydrobromic acid at the reflux temperature. This reaction, which yields 10 the corresponding compounds of formula XI, is usually carried out for a period of about 2 hours.

For those compounds of the formula X wherein Q is a group of the formula VII or VIII, it is preferable to remove the methoxybenzyl group by treating them with hydrogen in 15 the presence of a metal containing catalyst such as platinum or palladium. Generally, this reaction is conducted in a reaction inert solvent such as acetic acid or a lower alcohol, at a temperature from about 0°C to about 50°C. (These compounds may also, alternatively, be treated with a 20 dissolving metal such as lithium or sodium in ammonia at a temperature from about -30°C to about -78°C, or with a formate salt in the presence of palladium or with cyclohexane in the presence of palladium). Preferably, such compounds are treated with hydrogen in the presence of 25 palladium on carbon in a mixture of methanol/ethanol in water or methanol/ethanol containing hydrochloric acid at a temperature of about 25°C.

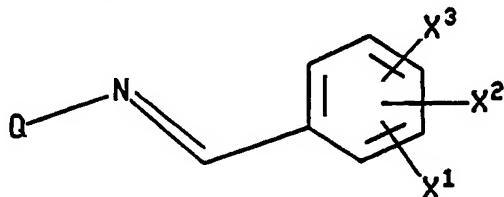
The resulting compounds of the formula XI may be converted to the corresponding compounds of the formula I by 30 reaction with the appropriate compound of the formula XII (as depicted in scheme 1). This reaction is typically carried out in the presence of a reducing agent such as sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, hydrogen and a metal catalyst, zinc and 35 hydrochloric acid, borane dimethylsulfide or formic acid at a temperature from about -60°C to about 50°C. Suitable reaction inert solvents for this reaction include lower

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alcohols (e.g., methanol, ethanol and isopropanol), acetic acid and tetrahydrofuran (THF). Preferably, the solvent is acetic acid, the temperature is about 25°C, and the reducing agent is sodium triacetoxyborohydride.

5 Alternatively, the reaction of a compound of the formula XI with a compound of the formula XII may be carried out in the presence of a drying agent or using an apparatus designed to remove azeotropically the water generated, to produce an imine of the formula

10

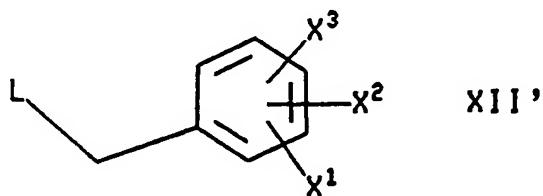


15

which is then reacted with a reducing agent as described above, preferably with sodium triacetoxyborohydride at about room temperature. The preparation of the imine is generally carried out in a reaction inert solvent such as benzene, 20 xylene or toluene, preferably toluene, at a temperature from about 25°C to about 110°C, preferably at about the reflux temperature of the solvent. Suitable drying agents/solvent systems include titanium tetrachloride/dichloromethane, titanium isopropoxide/dichloromethane and molecular 25 sieves/THF. Titanium tetrachloride/dichloromethane is preferred.

Compounds of the formula XI may also be converted to the corresponding compounds of the formula I by reaction with the appropriate compound of the formula

30



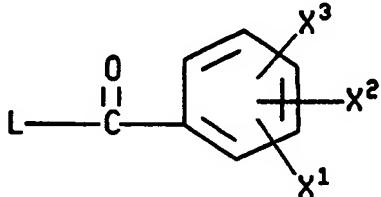
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wherein L is a leaving group (e.g., chloro, bromo, iodo, tosylate or mesylate). This reaction is generally carried out in a reaction inert solvent such as dichloromethane or THF, preferably dichloromethane, at a temperature from about 5 0°C to about 60°C, preferably at about 25°C.

Compounds of the formula XI may also be converted to the corresponding compounds of the formula I by reacting them with the appropriate compound of the formula

10



15 wherein L is defined as above or is imidazole, and then reducing the resulting amide. This reaction is typically carried out in an inert solvent such as THF or dichloromethane at a temperature from about -20°C to about 60°C, preferably in dichloromethane at about 0°C. Reduction 20 of the resulting amide is accomplished by treatment with a reducing agent such as borane dimethylsulfide complex, lithium aluminum hydride or diisobutylaluminum hydride in an inert solvent such as ethyl ether or THF. The reaction temperature may range from about 0°C to about the reflux 25 temperature of the solvent. Preferably, the reduction is accomplished using borane dimethylsulfide complex in THF at about 60°C.

When Q is a group of the formula II, the starting 30 materials of the formula X may be prepared as described in United States Patent Application Serial No. 566,338, filed July 20, 1990 and assigned to Pfizer Inc. This application is incorporated herein in its entirety.

When Q is a group of the formula III, the starting 35 materials of the formula X may be prepared as described in United States Patent Application Serial No. 532,525, filed June 1, 1990 and the PCT patent application claiming

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priority from it that was filed April 25, 1991 and is entitled "3-Amino-2-Aryl Quinuclidines." Both these applications are assigned to Pfizer Inc. and are incorporated herein in their entirety.

5 When Q is a group of the formula IV, V or VI, the starting materials of the formula X may be prepared as described in United States Patent Application Serial No. 557,442, filed July 23, 1990 and the PCT patent application claiming priority from it that was filed May 15, 1991, and
10 10 is entitled "Quinuclidine Derivatives." Both these applications are assigned to Pfizer Inc. and are incorporated herein in their entirety.

When Q is a group of the formula VII, the starting materials of the formula X may be prepared as described in
15 the following patent applications, all of which are assigned to Pfizer Inc: United States Patent Application Serial No. 619,361, filed November 28, 1990; United States Patent Application Serial No. 675,244, filed March 26, 1991; United States Patent Application Serial No. 800,667, filed on
20 November 27, 1991; and PCT Patent Application Serial No. PCT/US 92/00065, which designates the United States and was filed on January 4, 1992. The foregoing four applications are incorporated herein in their entirety.

When Q is a group of the formula VIII, the starting materials of the formula X may be prepared as described in United States Patent Application Serial No. 590,423, filed September 28, 1990 and assigned to Pfizer Inc. This application is incorporated herein in its entirety.

Scheme 2 illustrates an alternate method of preparing
30 compounds of the formula I wherein Q is a group of the formula VII.

As shown in Scheme 2, reductive amination of a compound of the formula XII with sodium cyanoborohydride or sodium triacetoxyborohydride and a compound of the formula XIII
35 yields a compound of the formula XIV. This reaction is typically carried out in a polar solvent such as acetic acid or a lower alkanol, at a temperature from about 0°C to about

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50°C. Methanol is the preferred solvent and about 25°C is the preferred temperature. It is also preferable that the pH of the reaction mixture be from about 4 to about 5.

Reduction of the compound of formula XIV yields a
5 compound of the formula I wherein Q is a group of the
formula VII and m is zero. Suitable reducing agents include
borane dimethylsulfide in THF, lithium aluminum hydride,
borane in THF and sodium borohydride-titanium (IV) chloride.
Best results are obtained by using borane dimethylsulfide in
10 THF. The reaction may be carried out at temperatures from
about room temperature to about 150°C, and is preferably
carried out at the reflux temperature of the solvent.

The compounds of formula I so formed may be converted
to a compound of the formula I wherein Q is a group of the
15 formula VII and m is other than zero having the same
stereochemistry by reacting them with the appropriate
compound of the formula $R^{10}-(CH_2)_m-L'$, wherein L' is halo,
mesylate or tosylate and wherein one of the carbon-carbon
single bonds of said $(CH_2)_m$ may optionally be replaced by a
20 carbon-carbon double bond or a carbon-carbon triple bond,
and wherein one of the carbons of said $(CH_2)_m$ may optionally
be substituted with R¹¹. This reaction is typically carried
out in the presence of a base such as triethylamine or
potassium t-butoxide, in a polar solvent such as methylene
25 chloride or dichloroethane, and at a temperature from about
room temperature to about 150°C. Preferably, the reaction
is carried out at the reflux temperature in methylene
chloride in the presence of triethylamine.

The starting materials of the formula XIII may be
30 prepared as described in United States Patent Application
Serial No. 619,361, filed November 28 1990 and assigned to
Pfizer Inc. This application is incorporated herein in its
entirety.

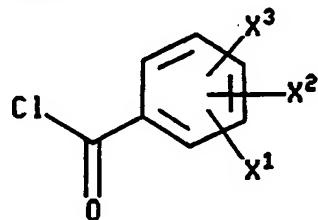
Scheme 3 illustrates an alternate method of making
35 compounds of the formula I wherein Q is a group of the
formula VIII.

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As shown in scheme 3, reductive amination of a compound of the formula XII in the presence of a compound of the formula XV yields a compound of the formula XVI. Examples of reducing agents that may be used are hydrogen in the presence of a metal catalyst, sodium borohydride, sodium cyanoborohydride and sodium triacetoxyborohydride. This reaction is generally carried out in a polar solvent such as acetic acid or a lower alkanol, in the presence of a dehydrating agent such as molecular sieves, at a temperature from about 0 to about 50°C. Methanol is the preferred solvent and 25°C is the preferred temperature. It is also preferable that the pH of the reaction mixture be from about 4 to about 5.

Alternatively, compounds of the formula XVI may be formed by acylating a compound of the formula XV with a compound having the formula

20



and then reducing the resulting amide. The acylation is generally conducted in a polar solvent (e.g., dichloromethane, THF or ethyl ether), at a temperature from about 0 to about 60°C. The preferred solvent is dichloromethane and the preferred temperature is about 25°C. Examples of reducing agents that may be used to reduce the amide are lithium aluminum hydride and borane dimethyl sulfide. The reduction is typically carried out in a polar solvent (e.g., ether, THF or DME) at a temperature from about 0°C to about the reflux temperature of the solvent, preferably at about room temperature.

The compounds of formula XVI may be converted into the corresponding compounds of formula I wherein Q is a group of the formula VIII and m is zero by reacting them with ammonium formate in the presence of palladium on charcoal

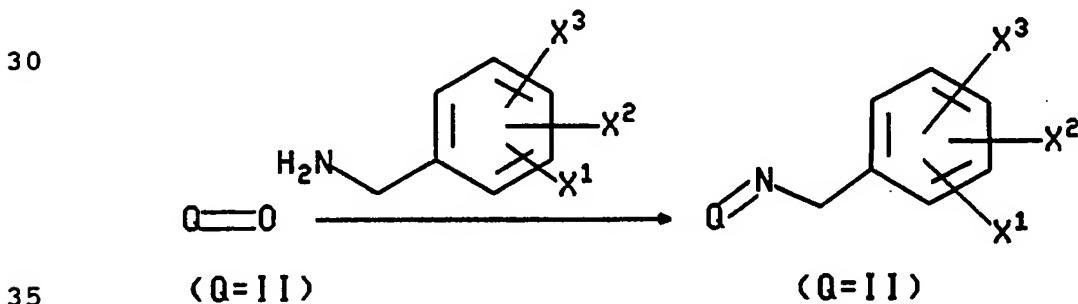
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(e.g., 10% palladium on charcoal). Usually, a polar solvent such as ethyl acetate or a lower alkanol is used, and the reaction is run at a temperature from about room temperature to about 150°C for about 0.5 to about 24 hours. Preferably, 5 the reaction is conducted in ethanol at room temperature for about 3 to about 24 hours.

The compounds of the formula I prepared by the foregoing procedure may be converted into compounds that are identical but for the fact that m is not equal to zero using
10 the procedure described above for preparing compounds of the formula I wherein Q is a group of the formula VII and m is not equal to zero.

The starting materials of the formula XV may be prepared as described in United States Patent application 15 Serial No. 590,423, filed September 28, 1990 and assigned to Pfizer Inc. This application is incorporated herein in its entirety.

Compounds of Formula I wherein Q is a group of the formula II and there is a double bond between Q and the adjacent nitrogen are prepared as shown below by condensation of Q=O (Q of formula II) with the appropriate benzylamine. The condensation is typically carried out in a nonhydroxylic solvent such as benzene, toluene or THF using an acid such as methanesulfonic acid or p-toluenesulfonic acid at a temperature from about 20°C to the reflux temperature of the solvent. Preferably, the reaction is carried out using camphorsulfonic acid in toluene at reflux.



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The preparation of other compounds of the formula I not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in 5 the art.

In each of the reactions discussed or illustrated in schemes 1 to 3 above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient 10 pressure, i.e. about 1 atmosphere, is preferred as a matter of convenience.

The novel compounds of the formula I and the pharmaceutically acceptable salts thereof are useful as substance P antagonists, i.e., they possess the ability to 15 antagonize the effects of substance P at its receptor site in mammals, and therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The compounds of the formula I which are basic in 20 nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the Formula I from the 25 reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid 30 addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful 35 evaporation of the solvent, the desired solid salt is readily obtained.

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Those compounds of the formula I which are also acidic in nature, e.g., where R¹ is carboxyphenyl, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or
5 alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base
10 salts with the acidic compounds of formula I. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with
15 an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired
20 alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

25 The compounds of formula I and their pharmaceutically acceptable salts exhibit substance P receptor-binding activity and therefore are of value in the treatment and prevention of a wide variety of clinical conditions the treatment or prevention of which are effected or facilitated
30 by a decrease in substance P mediated neurotransmission. Such conditions include inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, gastroesophageal reflux disease,
35 allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and

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Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related 5 somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and 10 rheumatic diseases such as fibrositis. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

15 The compounds of the formula I and the pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 5.0 mg up to about 1500 mg per day, although 20 variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably 25 employed. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In 30 some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration 35 throughout the day.

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable

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carriers or diluents by either of the three routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be
5 administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions,
10 ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or
15 flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various
20 excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with
25 granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as
30 fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with
35 various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water,

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ethanol, propylene glycol, glycerin and various like combinations thereof.

- For parenteral administration, solutions of a therapeutic compound of the present invention in either 5 sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for 10 intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.
- 15 Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical 20 practice.

The activity of the compounds of the present invention as substance P antagonists may be determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate tissue, employing 25 radioactive ligands to visualize the tachykinin receptors by means of autoradiography. The substance P antagonizing activity of the herein described compounds may be evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological 30 Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic 35 IC₅₀ values for each compound tested.

In this procedure, bovine caudate tissue is removed from a -70°C freezer and homogenized in 50 volumes (w./v.)

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of an ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at 30,000 x G for a period of 20 minutes. The pellet is
5 resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at 30,000 x G for another twenty- minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 40 g/ml of
10 bacitracin, 4 μ g/ml of leupeptin, 2 μ g of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction
15 via the addition of 100 μ l of the test compound made up to a concentration of 1 μ M, followed by the addition of 100 μ l of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800 μ l of the tissue preparation produced as described above.
20 The final volume is thus 1.0 ml, and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM of Tris buffer (pH
25 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC₅₀ values are calculated by using standard statistical methods.

30 The anti-psychotic activity of the compounds of the present invention as neuroleptic agents for the control of various psychotic disorders may be determined by a study of their ability to suppress substance P-induced or substance P agonist induced hypermotility in guinea pigs. Such a
35 study may be carried out by first dosing the guinea pigs with a control compound or with an appropriate test compound of the present invention, then injecting the guinea pigs with

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substance P or a substance P agonist by intracerebral administration via canula and thereafter measuring their individual locomotor response to said stimulus.

The present invention is illustrated by the following 5 examples. It will be understood, however, that the invention is not limited to the specific details of these examples.

EXAMPLE 1

2-(Diphenylmethyl)-N-((2-difluoromethoxy)phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine

10 A. 2-(Difluoromethoxy)benzaldehyde:

To a 500 mL three-necked round-bottomed flask equipped with condenser and gas inlet tube were added 5.0 g (40.98 mmol) salicylaldehyde, 150 mL dioxane, and 150 mL (164 mmol) of a 1.1 N aqueous solution of sodium hydroxide. 15 Chlorodifluoromethane gas was bubbled through the reaction mixture as it was heated to 60°C, and the reaction mixture was stirred at this temperature for 2 hours. The reaction mixture was then cooled and extracted with ether. The organic layer was dried over sodium sulfate, filtered and 20 evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford a light yellow oil, 1.63 g (23%).

¹H NMR (δ , CDCl₃): 6.64 (t, J=72.7 (H-F), 1H), 7.16 (d, J=7, 1H), 7.24 (t, J=7, 1H), 7.53 (m, 1H), 7.81 (m, 1H), 25 10.29 (s, 1H).

¹³C-NMR (CDCl₃): 112.2, 115.6, 115.645, 115.7, 119.1, 119.2, 119.5, 125.6, 125.7, 125.8, 125.9, 127.5, 128.8, 128.9, 135.7, 152.71, 152.73, 188.4.

IR (cm⁻¹, neat): 1700 (C=O).

30 MS (%): 172 (100, parent), 171 (48), 122 (45), 121 (82), 120 (69), 104 (37), 95 (40), 92 (55), 91 (49), 76 (39), 65 (49), 63 (76), 51 (81).

Anal. Calc'd for C₈H₆F₂O₂•1/4H₂O: C 54.50, H 3.71. Found: C 54.68, H 3.33.

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B. 2-(Diphenylmethyl)-N-((2-difluoromethoxy)-phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine

To a 25 mL round-bottomed flask equipped with a nitrogen inlet were added 500 mg (1.71 mmol) 2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine (prepared according to the method of Warawa, *et al.*, *J. Med. Chem.*, 17, 497 (1974)), 8.5 mL methanol, 383 mg (2.23 mmol) 2-(difluoromethoxy)-benzaldehyde, and 216 mg (3.42 mmol) sodium cyanoborohydride. The reaction was stirred at room temperature for 30 hours, partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated. To remove the last traces of unreacted amine, the mixture was treated with sodium triacetoxyborohydride in acetic acid at room temperature for 16 hours, then worked up with aqueous sodium hydroxide and methylene chloride. The residue was crystallized from isopropanol to afford a white solid, m.p. 144-147°C, 206 mg (27%).

¹H NMR (δ , CDCl₃): 1.27 (m, 1H), 1.4-1.8 (m, 2H), 1.90 (m, 1H), 2.05 (m, 1H), 2.63 (m, 1H), 2.78 (m, 2H), 2.88 (m, 1H), 3.19 (m, 1H), 3.45 (AB_q, J_{AB}=13.5, $\Delta\nu$ =105.5, 2H), 3.72 (dd, J=8, 12, 1H), 4.43 (d, J=12, 1H), 6.31 (t, J=74 (H-F), 1H), 6.55 and 7.0-7.4 (m, 14H).

¹³C-NMR (CDCl₃): 20.0, 24.9, 25.4, 42.0, 45.8, 49.4, 49.5, 55.0, 61.8, 116.3, 119.0, 125.4, 126.0, 126.5, 127.5, 127.8, 127.9, 128.0, 128.4, 128.5, 128.6, 129.1, 129.2, 130.0, 131.6, 143.2, 145.2, 149.3.

IR (cm⁻¹, neat): 2940 (C-H), 1599 (C=C).

MS (%): 449 (<1, parent+1), 291 (51), 281 (100), 84 (66), 49 (69).

Anal. Calc'd for C₂₈H₃₀F₂N₂O: C 74.98, H 6.74, N 6.25.

Found: C 74.72, H 6.70, N 6.23.

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EXAMPLE 2

(2S,3S)-N-(2-Methoxy-5-trifluoromethoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-amine methanesulfonic acid salt

5 The title compound was prepared in a manner similar to the procedure described in Example 1, by replacing 2-(difluoromethoxy)benzaldehyde with 2-methoxy-5-trifluoromethoxybenzaldehyde in Step B.

M.p. 135°C.

10 ^1H NMR (CDCl_3) δ 1.8-2.3 (m, 2H), 2.2-2.8 (m, 6H), 2.66 (s, 6H), 3.56 (s, 3H), 3.3-3.7 (m, 3H), 3.90 (m, 3H), 4.16 (m, 2H), 5.06 (m, 1H), 5.20 (br, 1H), 5.50 (m, 1H), 5.60 (br, 1H), 6.77 (d, 1H, $J=9.2$), 7.02 (m, 1H), 7.2-7.8 (m, 11H), 8.00 (br, 1H), 10.8 (br, 1H).

15 IR (cm^{-1} , KBr): 3180, 3140, 3000, 1500, 1200, 1062, 782.

EXAMPLE 3

(2S,3S)-2-Phenyl-3-[2-(2,2,2-trifluoroethoxy)benzyl]-aminopiperidine hydrochloride

A. 2-(2,2,2-Trifluoroethoxy)benzaldehyde

20 Under a nitrogen atmosphere in a round-bottom flask equipped with a reflux condenser were placed 0.2 g (1 mmol) of 2-(2,2,2-trifluoroethoxy)benzonitrile (J. Org. Chem., 377 (1983)) and 5 mL of formic acid. To this solution was added ca. 0.2 g of Raney nickel, and the mixture was heated at reflux for 90 minutes. The mixture was filtered through diatomaceous earth, and the filter cake was rinsed with water and chloroform (CHCl_3). The layers were separated, and the aqueous phase was extracted with three portions of chloroform. The combined organic fractions were washed with saturated aqueous sodium bicarbonate and water, dried over sodium sulfate (Na_2SO_4) and concentrated (rotary evaporator) to obtain 176 mg of the title compound as a yellow solid, m.p. 33-34°C.

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B. (2S,3S)-2-Phenyl-3-[2-(2,2,2-trifluoroethoxy)-benzyl]aminopiperidine hydrochloride

Under a nitrogen atmosphere in a round-bottom flask were placed 112 mg (0.63 mmol) of (2S, 3S)-3-amino-2-phenylpiperidine, 155 mg (0.76 mmol) of the aldehyde prepared in step A above and ca. 2 mL of acetic acid, and the solution was stirred at room temperature for 1 hour. To the system were added 294 mg (1.39 mmol) of sodium triacetoxylborohydride in portions, and the mixture was 10 stirred at room temperature overnight. The mixture was concentrated with a rotary evaporator and partitioned between 1M aqueous sodium hydroxide (NaOH) and methylene chloride (CH_2Cl_2). The layers were separated, and the aqueous phase was extracted with three portions of CH_2Cl_2 . 15 The combined organic fractions were extracted with three portions of 2N aqueous HCl, the extracts were made basic with 2N aqueous NaOH, and the mixture was extracted with four portions of CH_2Cl_2 . These CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated. The resulting oil was dissolved 20 in ca. 2 mL ethyl acetate and treated with ether saturated with hydrogen chloride (HCl). The resulting white solid (73 mg, m.p. > 275°C) was collected. This material was converted to its free base by partitioning between 1N aqueous NaOH and CH_2Cl_2 . The free base (58 mg) was purified 25 by flash column chromatography eluting with chloroform (CHCl_3) followed by 1:19 methanol/ CHCl_3 , to obtain 32 mg of oil. Conversion of the free base to the corresponding hydrochloride salt as described above afforded 17 mg of the title compound, m.p. > 275°C.

30 ^1H NMR (free base, CDCl_3) δ 1.44 (m, 1H), 1.63 (m, 1H), 1.88 (m, 1H), 2.1 (m, 1H), 2.80 (m, 2H), 3.26 (m, 1H), 3.38 (d, 1H, J=15), 3.66 (d, 1H, J=15), 3.88 (s, 1H), 4.08 (m, 2H), 6.68 (d, 1H, J=6), 6.90 (m, 1H), 6.98 (d, 1H, J=6), 7.16 (m, 1H), 7.26 (m, 5H).

35 HRMS Calc'd for $\text{C}_{20}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_3$ (parent + 1): 365.1835.
Found: 365.1980.

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Anal. Calc'd for $C_{20}H_{23}F_3N_2O \cdot 2HCl \cdot 1/3H_2O$: C, 54.19, H, 5.84; N, 6.32. Found: C, 54.22, H, 5.57, N, 6.28.

EXAMPLE 4

(2S,3S)-3-(2-Methoxy-5-trifluoromethoxybenzyl)amino-2-

5 phenylpiperidine hydrochloride salt

A. 2-Methoxy-5-trifluoromethoxybenzaldehyde

Under a nitrogen atmosphere in a round-bottom flask were placed 3.63 mL (28 mmol) of 4-trifluoromethoxyphenol and 25 mL of acetone. To this stirring solution were added 10 7.75 g (56 mmol) of potassium carbonate and 3.48 mL (56 mmol) of methyl iodide, and the reaction mixture was stirred at room temperature overnight. The solids were removed by suction filtration and the filter cake was rinsed with acetone. The filtrate was concentrated to obtain 6.5 g of 15 a solid/oil mixture. This mixture was diluted with $CHCl_3$ and filtered and the filtrate was concentrated to afford 5.5 g of 1-methoxy-4-trifluoromethoxybenzene as a yellow oil.

1H NMR ($CDCl_3$) δ 3.78 (s, 3H), 6.83 (d, 1H, $J=12$), 7.10 (d, 1H, $J=12$). Mass spectrum m/z: 192 (parent).

20 Under a nitrogen atmosphere in a round-bottom flask were placed the 1-methoxy-4-trifluoromethoxybenzene (5.5 g, 29 mmol) and 110 mL of CH_2Cl_2 . To the system, cooled in an ice/acetone bath, were added 3.77 mL (34 mmol) of titanium tetrachloride ($TiCl_4$) over a period of ca. 1 minute. The 25 reaction mixture was stirred for 30 minutes and 5.69 mL (63 mmol) of α,α -dichloromethylmethyl ether was added to the system. The ice bath was allowed to expire and the mixture was stirred at room temperature overnight. The mixture was 30 poured carefully into water and extracted with three portions of CH_2Cl_2 . These combined extracts were washed with water and brine, dried (Na_2SO_4) and concentrated to obtain 6.06 g of an oil. The crude material was purified by flash column chromatography (250 g of silica gel) using 1:9 ethyl acetate/hexanes as the eluant to obtain 920 mg of the title 35 compound with a slight impurity and 3.27 g of pure title compound.

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¹H NMR (CDCl₃) δ 3.94 (s, 3H), 7.00 (d, 1H, J=9), 7.38 (dd, 1H, J=3, 9), 7.66 (d, 1H, J=3), 10.4 (s, 1H). Mass spectrum m/z: 220 (parent).

5 B. (2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)-
5 amino-2-phenylpiperidine hydrochloride salt

Under a nitrogen atmosphere in a round-bottom flask were placed 525 mg (2.4 mmol) of 2-methoxy-5-trifluoromethoxybenzaldehyde, 350 mg (2.0 mmol) of (2S, 3S)-3-amino-2-phenylpiperidine and 5 mL of acetic acid. The 10 reaction mixture was stirred at room temperature for 3 days and concentrated with a rotary evaporator. The residue was partitioned between 1N aqueous sodium hydroxide and chloroform (CHCl₃) and the mixture was extracted with three portions of chloroform. The combined chloroform extracts 15 were extracted with three portions of 1N aqueous hydrochloric acid. The combined HCl extracts were made basic with concentrated aqueous sodium hydroxide and extracted with four portions of chloroform. The chloroform extracts were dried (Na₂SO₄) and concentrated with a rotary 20 evaporator to obtain 760 mg of an oil. The oil was dissolved in ethyl acetate, and ether saturated with hydrogen chloride (HCl) was added to the solution. The resulting white solid was collected by suction filtration and washed with ether to obtain 600 mg of the title 25 compound, m.p. > 250°C.

¹H NMR (free base, CDCl₃) δ 1.36 (s, 1H), 1.54 (m, 1H), 1.86 (m, 1H), 2.06 (m, 1H), 2.76 (m, 2H), 3.22 (m, 1H), 3.32 (d, 1H, J=15), 3.48 (s, 3H), 3.58 (d, 1H, J=15), 3.85 (d, 1H, J=3), 6.57 (d, 1H, J=9), 6.80 (d, 1H, J=3), 6.92 (dd, 1H, J=3, 9), 7.22 (m, 5H).

HRMS Calc'd for C₂₀H₂₃F₃N₂O₂: 380.1711. Found: 380.1704.

Anal. Calc'd for C₂₀H₂₃F₃N₂O₂•2HCl•0.2H₂O: C 52.57, H 5.60, N 6.13. Found: C 52.58, H 5.40, N 5.97.

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EXAMPLE 5

(2S,3S)-1-(5,6-Dimethoxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine hydrochloride

Under a nitrogen atmosphere in a round-bottom flask
5 were placed 250 mg (0.66 mmol) of (2S, 3S)-3-(2-methoxy-5-
trifluoromethoxybenzyl)amino-2-phenylpiperidine, 2 mL of
tetrahydrofuran (THF) and 0.28 mL (2.0 mmol) of
triethylamine. To the system were added 475 mg (2.0 mmol)
of 5,6-dimethoxy-1-methylsulfonyloxyhexane (prepared from
10 1,5,6-hexanetriol by sequential acetonide formation
(acetone, p-toluenesulfonic acid), acetylation (acetyl
chloride, triethylamine, THF), acetonide cleavage (60%
acetic acid/water), dimethylation (sodium hydride, methyl
iodide, THF), deacetylation (sodium methoxide, methanol) and
15 methanesulfonate ester formation (methanesulfonyl chloride,
triethylamine, THF)), and the mixture was heated at 50-60°C
for four days. The reaction mixture was partitioned between
CHCl₃, and saturated aqueous sodium bicarbonate and extracted
with three portions of CHCl₃. The combined organic fractions
20 were dried (Na₂SO₄), filtered and concentrated to obtain 853
mg of an orange oil. The crude material was purified by
flash column chromatography (35 g of silica gel) using 1:19
methanol/chloroform as the eluant to obtain 185 mg of yellow
oil. The oil was dissolved in ethyl acetate and ether
25 saturated with HCl was added to the solution. The mixture
was concentrated and the residue was triturated with ether
to obtain 190 mg of the title compound.

¹H NMR (free base, CDCl₃) δ 1.15 (m, 2H), 1.38 (m, 6H),
1.76 (m, 2H), 1.96 (m, 3H), 2.50 (m, 2H), 3.16 (m, 2H), 3.26
30 (m, 9H), 3.46 (s, 3H), 3.58 (d, 1H, J=15), 6.52 (d, 1H,
J=9), 6.69 (m, 1H), 6.86 (m, 1H), 7.22 (m, 5H).

HRMS calc'd for C₂₈H₃₉F₃N₂O₄: 524.28616. Found:
524.28634.

Anal. Calc'd for C₂₈H₃₉F₃N₂O₄•2HCl•0.75H₂O: C 55.03, H
35 7.00, N 4.58. Found: C 55.04, H 7.12, N 4.51.

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EXAMPLE 6

(2S,3S)-2-Phenyl-3-(2-trifluoromethoxybenzyl)amino-piperidine hydrochloride salt

Under a nitrogen atmosphere in a round-bottom flask
5 were placed 3.0 mL (23 mmol) of trifluoromethoxybenzene and
25 mL of benzene. The system was cooled in ice/acetone
bath, and 4.1 mL (45 mmol) of α,α -dichloromethylmethyl ether
was added to the stirring solution. To the system was added
6.13 g (46 mmol) of aluminum chloride ($AlCl_3$) in portions.
10 After this addition was complete, the reaction mixture was
allowed to warm gradually to room temperature and stirred at
room temperature overnight. The reaction mixture was poured
slowly into water and extracted with three portions of
dichloromethane. The combined organic fractions were washed
15 with water, dried (Na_2SO_4) and concentrated with a rotary
evaporator to obtain 3.7 g of oil. This material,
containing a mixture of 4- and 2-
trifluoromethoxybenzaldehyde, was subjected to flash column
chromatography (160 g of silica gel) using 1:49 ethyl
20 acetate/hexanes as the eluant to obtain 500 mg of material
enriched in 2-trifluoromethoxy-benzaldehyde.

Under a nitrogen atmosphere in a round-bottom flask
were placed 155 mg (0.88 mmol) of (2S,3S)-3-amino-2-
phenylpiperidine, the aldehyde obtained above and 2 mL of
25 acetic acid. To the system were added 370 mg (1.8 mmol) of
sodium triacetoxyborohydride and the mixture was stirred at
room temperature overnight. The mixture was concentrated
and the residue was partitioned between 1N aqueous sodium
hydroxide and dichloromethane and extracted with three
30 portions of dichloromethane. The combined organic fractions
were extracted with three portions of 1N HCl. The acid
extracts were made basic with 1N aqueous NaOH and extracted
with three portions of dichloromethane. The dichloromethane
extracts were dried and concentrated to afford 190 mg of
35 oil, which was subjected to flash column chromatography (5
g of silica gel) using 1:9 methanol/chloroform as the eluant
to obtain 95 mg of the free base of the title compound. The

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free base was dissolved in ethyl acetate, and ether saturated with HCl was added to the solution. The resulting white solid was collected by suction filtration and rinsed with ether to obtain 72 mg of the title compound, m.p. 231-
5 233°C.

10 ¹H NMR (free base, CDCl₃) δ 1.40 (m, 1H), 1.60 (m, 1H), 1.84 (m, 1H), 2.05 (m, 1H), 2.78 (m, 2H), 3.22 (m, 1H), 3.42 (d, 1H, J=15), 3.56 (d, 1H, J=15), 3.86 (d, 1H, J=3), 7.08 (m, 4H), 7.24 (m, 5H). Mass spectrum: m/z 350 (parent).
15 Anal. Calc'd for C₁₉H₂₁F₃N₂O•2HCl•0.25H₂O: C 53.34, H 5.54, N 6.54. Found: C 53.19, H 5.40, N 6.54.

EXAMPLE 7

20 (2S,3S)-3-(2-Hydroxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine Hydrochloride

25 A. 2-Hydroxy-5-trifluoromethoxybenzaldehyde
Under a nitrogen atmosphere, in a round-bottom flask were placed 300 mg (1.4 mmol) of 2-methoxy-5-trifluoromethoxybenzaldehyde and 30 ml of dichloromethane. To the system, cooled in a dry ice acetone bath, were added 0.26 ml (2.7 mmol) of boron tribromide (BBr₃) over a period of ca. 1 minute. The reaction mixture was stirred for 1 hour, the dry ice/acetone bath was replaced with an ice bath and the mixture was stirred for 1 hour. To the system were added slowly 10 ml of saturated aqueous sodium bicarbonate followed by 10 ml of water, and the mixture was warmed to room temperature. The mixture was extracted with two portions of dichloromethane, and the extracts were dried (Na₂SO₄) and concentrated. The resulting oil (280 mg) was dissolved in CH₂Cl₂, and the solution was extracted with two portions of 1M aqueous NaOH. The combined aqueous extracts were acidified with 2M aqueous HCl and extracted with three portions of dichloromethane. These dichloromethane extracts were dried (Na₂SO₄) and concentrated to obtain 200 mg of the title compound.

35 ¹H NMR (CDCl₃) δ 6.96 (d, 1H, J=9), 7.36 (m, 2H), 9.84 (s, 1H), 10.9 (s, 1H).

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B. (2S,3S)-3-(2-Hydroxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine Hydrochloride

The title compound was prepared in a manner similar to the compound of Example 4 by replacing 2-methoxy-5-
5 trifluoromethoxybenzaldehyde with 2-hydroxy-5-trifluoromethoxybenzaldehyde.

¹H NMR (free base, CDCl₃) δ 1.60 (m, 3H), 2.04 (m, 1H),
2.76 (m, 1H), 2.88 (m, 1H), 3.18 (m, 1H), 3.42 (s, 2H), 3.90
10 (m, 1H), 6.52 (m, 1H), 6.64 (d, 1H, J=9), 6.89 (m, 1H), 7.30
(m, 5H).

HRMS calc'd for C₁₉H₂₁F₃N₂O₂: 366.1545. Found: 366.1562.

Anal. calc'd for C₁₉H₂₁F₃N₂O₂•2HCl•1/3H₂O: C, 51.25; H,
4.90; N, 6.29. Found: C, 51.30; H, 4.75; N, 6.22.

EXAMPLE 8

15 (2S,3S)-3-(5-Chloro-2-[2,2,2-trifluoroethoxy]benzyl)-amino-2-phenylpiperidine Hydrochloride

A. 5-Chloro-2-(2,2,2-trifluoroethoxy)benzaldehyde

Under a nitrogen atmosphere, in a round-bottom flask were placed 880 mg (22 mmol) of 60% sodium hydride (NaH) and
20 12 ml of N,N-dimethylformamide. To the system were added 2.9 ml (4 g, 40 mmol) of 2,2,2-trifluoroethanol via syringe over a period of 15 minutes and the mixture was stirred at room temperature for 20 minutes. To the system were added 1.72 g (10 mmol) of 2,5-dichlorobenzonitrile, and the
25 mixture was heated at 90°C for three days. The mixture was cooled to room temperature, poured into 50 ml of 2M aqueous HCl and extracted with three portions of ether. The combined organic fractions were dried (Na₂SO₄) and concentrated to afford 2.5 g of a solid. The crude material
30 was purified by flash column chromatography using 1:49 ethyl acetate/hexanes as the eluant to obtain 1.4 g of 5-chloro-2-(2,2,2-trifluoroethoxy)benzonitrile as a white solid.

M.p. 61-62°C.

Under a nitrogen atmosphere, in a round-bottom flask equipped with a reflux condenser were placed 400 mg (1.7 mmol) of the above nitrile and 10 ml of formic acid. To the system were added ca. 500 mg of Raney nickel and the

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mixture was heated at reflux for 6 hours and stirred at room temperature overnight. The mixture was filtered through a pad of a diatomaceous earth, and the pad was rinsed with water and CHCl₃. The layers were separated and the aqueous phase was extracted with three portions of CHCl₃. The combined organic fractions were dried and concentrated to obtain 270 mg of the title compound.

¹H NMR (CDCl₃) δ 4.42 (m, 2H), 6.86 (d, 1H, J=10), 7.46 (m, 1H), 7.80 (d, 1H, J=3), 10.3 (s, 1H).

10 Mass spectrum: m/z 238 (parent).

B. (2S,3S)-3-(5-Chloro-2-[2,2,2-trifluoroethoxy]benzyl)amino-2-phenylpiperidine Hydrochloride

The title compound was prepared in a manner similar to the procedure described in Example 4 by replacing 2-methoxy-15 5-trifluoromethoxybenzaldehyde with 5-chloro-2-(2,2,2-trifluoroethoxy)benzaldehyde.

M.p. 267-269°C.

¹H NMR (free base, CDCl₃) δ 1.4 (m, 1H), 1.6 (m, 1H), 1.82 (m, 1H), 2.02 (m, 1H), 2.78 (m, 2H), 3.2 (m, 1H), 3.3 20 (d, 1H, J=15), 3.54 (d, 1H, J=15), 3.84 (d, 1H, J=3), 4.0 (m, 2H), 6.54 (d, 1H, J=10), 6.92 (d, 1H, J=3), 7.04 (m, 1H), 7.24 (m, 5H).

Anal. calc'd for C₂₀H₂₂ClF₃N₂O•2HCl: C, 50.91; H, 5.13; N, 5.94. Found: C, 50.89; H, 4.84; N, 5.93.

25 EXAMPLE 9

(2S,3S)-2-Phenyl-3-(3-trifluoromethoxybenzyl)aminopiperidine Hydrochloride

The title compound was prepared in a manner similar to the procedure described in Example 4 by replacing 2-methoxy-30 5-trifluoromethoxybenzaldehyde with 3-trifluoromethoxybenzaldehyde.

M.p. > 275°C.

¹H NMR (free base, CDCl₃) δ 1.4 (m, 1H), 1.56 (m, 1H), 1.78 (m, 1H), 1.96 (m, 1H), 2.76 (m, 2H), 3.18 (m, 1H), 3.30 35 (d, 1H, J=15), 3.46 (d, 1H, J=15), 3.84 (d, 1H, J=3), 6.79 (s, 1H), 6.85 (d, 1H, J=6), 6.94 (m, 1H), 7.12 (m, 1H), 7.24 (m, 5H).

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Anal. calc'd for C₁₉H₂₁F₃N₂O•2HCl: C, 53.91; H, 5.48; N, 6.62. Found: C, 53.84; H, 5.07; N, 6.59.

The title compounds of Examples 10-23 and 26 were prepared in a manner similar to the procedure described in Example 4, by replacing 2-methoxy-5-trifluoromethoxybenzaldehyde with the appropriate aldehyde. Reaction sequences for the preparation of the requisite aldehydes are set forth in Table 1 below.

TABLE 1
Preparation of Compounds of the Formula XII

$-C_6H_2X_1X_2X_3$	Starting Material	Reaction* Sequence
2-(2,2,2-trifluoroethoxy)phenyl	2-chlorobenzonitrile	d, e
2-hydroxy-5-trifluoromethoxyphenyl	2-methoxy-5-trifluoromethoxybenzaldehyde	f
3-trifluoromethoxyphenyl	-	commercial
5-chloro-2-(2,2,2-trifluoroethoxy)-phenyl	2,5-dichlorobenzonitrile	d, e
5-t-butyl-2-trifluoromethoxyphenyl	trifluoromethoxybenzene	g, h
2-ethoxy-5-trifluoromethoxyphenyl	4-trifluoromethoxyphenol	i, a
2-difluoromethoxy-5-trifluoro-methoxyphenyl	2-hydroxy-5-trifluoromethoxybenzaldehyde	j
5-isopropyl-2-(2,2,2-trifluoroethoxy)phenyl	4-isopropyl-iodobenzene	d, a
2-isopropoxy-5-trifluoromethoxy-phenyl	4-trifluoromethoxyphenol	k, a
5-t-butyl-2-difluoromethoxyphenyl	4-t-butylphenol	a, j
2,5-bis(difluoromethoxy)phenyl	2,5-dihydroxybenzaldehyde	j
2-difluoromethoxy-5-dimethylamino-phenyl	5-amino-2-hydroxybenzaldehyde	l, j

TABLE 1
Preparation of Compounds of the Formula XII

$-C_6H_2X_1X_2X_3$	Starting Material	Reaction* Sequence
2-difluoromethoxy-5-isopropylphenyl	4-isopropylphenol	a, j
2-difluoromethoxy-5-nitrophenyl	2-hydroxy-5-nitrobenzaldehyde	j
5-dimethylamino-2-(2,2,2-trifluoroethoxy)phenyl	2-chloro-5-nitrobenzonitrile	d, l, e
5-acetamido-2-(2,2,2-trifluoroethoxy)phenyl	5-nitro-2-(2,2,2-trifluoroethoxy)benzonitrile	m, c, e
2-difluoromethoxy-5-ethylphenyl	4-ethyl-methoxybenzene	a, f, j
5-chloro-2-difluoromethoxyphenyl	5-chloro-2-hydroxybenzaldehyde	j
2-trifluoromethoxyphenyl	-	commercial
2-methoxy-5-trifluoromethoxyphenyl	4-trifluoromethoxyphenol	b, a
2-difluoromethoxy-5-methylphenyl	5-methyl-2-methoxybenzaldehyde	f, j

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*Reagents for Preparation of Compounds of the Formula XII
From Standard Routes

- a) $\text{Cl}_2\text{CHOCH}_3$, TiCl_4
- b) methyl iodide
- 5 c) acetyl chloride
- d) $\text{NaOCH}_2\text{CF}_3$
- e) Raney nickel, HCO_2H
- f) BBr_3
- 10 g) t-butyl chloride/ AlCl_3 ,
- h) $\text{Cl}_2\text{CHOCH}_3/\text{AlCl}_3$,
- i) ethyl iodide
- j) ClF_2CH
- k) isopropyl bromide
- 15 l) H_2 , Pd/C, HCHO
- m) $\text{H}_2\text{-Pd/BaSO}_4$

EXAMPLE 10

(2S,3S)-3-[5-Chloro-2-(2,2,2-trifluoroethoxy)benzyl]-amino-2-phenylpiperidine hydrochloride

M.P. 267-269°C.

20 ^1H NMR (free base; CDCl_3) δ 1.40 (m, 1H), 1.60 (m, 1H), 1.82 (m, 1H), 2.02 (m, 1H), 2.76 (m, 2H), 3.20 (m, 1H), 3.28 (d, 1H, $J=15$), 3.52 (d, 1H, $J=15$), 3.84 (d, 1H, $J=3$), 4.00 (m, 2H), 6.54 (d, 1H, $J=10$), 6.92 (d, 1H, $J=3$), 7.04 (m, 1H), 7.24 (m, 5H).

25 HRMS calc'd for $\text{C}_{20}\text{H}_{22}\text{ClF}_3\text{N}_2\text{O}$: 398.1368. Found: 398.1352.

Anal. calc'd for $\text{C}_{20}\text{H}_{22}\text{ClF}_3\text{N}_2\text{O} \cdot 2\text{HCl}$: C, 50.91; H, 5.13; N, 5.94. Found: C, 50.89; H, 4.84; N, 5.93.

EXAMPLE 11

30 (2S,3S)-3-(5-t-Butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine hydrochloride

M.P. 262-264°C.

^1H NMR (free Base; CDCl_3) δ 1.20 (s, 9H), 1.40 (m, 1H), 1.52 (m, 1H), 1.84 (m, 1H), 2.06 (m, 1H), 2.80 (m, 2H), 3.22 (m, 1H), 3.38 (d, 1H, $J=15$), 3.58 (d, 1H, $J=15$), 3.86 (d, 1H, $J=3$), 6.98 (m, 1H), 7.12 (m, 2H), 7.26 (m, 5H).

HRMS calc'd for $\text{C}_{23}\text{H}_{29}\text{F}_3\text{N}_2\text{O}$: 406.2225. Found: 406.2271.

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Anal. calc'd for $C_{23}H_{29}F_3N_2O \cdot 2HCl \cdot 1/3H_2O$: C, 56.92; H, 6.56; N, 5.77. Found: C, 56.99; H, 6.41; N, 6.03.

EXAMPLE 12

(2S,3S)-3-[5-Isopropyl-2-(2,2,2-trifluoroethoxy)-benzylamino-2-phenylpiperidine hydrochloride]

M.P. > 280°C.
 1H NMR (free base; $CDCl_3$) δ 1.12 (m, 6H), 1.4 (m, 1H), 1.62 (m, 1H), 1.82 (m, 1H), 2.08 (m, 1H), 2.76 (m, 3H), 3.22 (m, 1H), 3.30 (d, 1H, $J=15$), 3.38 (d, 1H, $J=15$), 3.82 (d, 1H, $J=3$), 4.02 (m, 2H), 6.56 (d, 1H, $J=10$), 6.78 (d, 1H, $J=3$), 6.94 (m, 1H), 7.24 (m, 5H).

HRMS calc'd for $C_{23}H_{30}F_3N_2O$ (M+1): 407.2303. Found: 407.2287.

Anal. calc'd for $C_{23}H_{29}F_3N_2O \cdot 2HCl \cdot 1/2H_2O$: C, 56.55, H, 6.60; N, 5.70. Found: C, 56.17; H, 6.39; N, 5.77.

EXAMPLE 13

(2S,3S)-3-[5-Dimethylamino-2-(2,2,2-trifluoroethoxy)-benzylamino-2-phenylpiperidine hydrochloride]

M.P. 250-252°C.
 1H NMR (free base; $CDCl_3$) δ 1.40 (m, 1H), 1.60 (m, 1H), 1.86 (m, 1H), 2.10 (m, 1H), 2.82 (m, 8H), 3.22 (m, 1H), 3.34 (d, 1H, $J=15$), 3.58 (d, 1H, $J=15$), 3.88 (d, 1H, $J=3$), 4.00 (m, 2H), 6.42 (d, 1H, $J=3$), 6.50 (m, 1H), 6.64 (d, 1H, $J=10$), 7.30 (m, 5H).

HRMS calc'd for $C_{22}H_{28}F_3N_3O$: 407.2178. Found: 407.2179.

EXAMPLE 14

(2S,3S)-3-(2-Difluoromethoxy-5-N,N-dimethylamino-benzyl)amino-2-phenylpiperidine hydrochloride

M.P. 243-245°C (dec).
 1H NMR (free base; $CDCl_3$) δ 1.44 (m, 1H), 1.72 (m, 2H), 2.10 (m, 1H), 2.84 (m, 8H), 3.21 (m, 1H), 3.28 (d, 1H, $J=15$), 3.55 (d, 1H, $J=15$), 3.88 (d, 1H, $J=3$), 6.08 (t, 1H, $J=72$), 6.36 (d, 1H, $J=3$), 6.46 (dd, 1H, $J=3,9$), 6.86 (d, 1H, $J=9$), 7.28 (m, 5H).

HRMS calc'd for $C_{21}H_{27}F_2N_3O$: 375.2122. Found: 375.2138.

Anal. calc'd for $C_{21}H_{27}F_2N_3O \cdot 3HCl \cdot 1/2H_2O$: C, 51.07; H, 6.44; N, 8.51. Found: C, 50.71; H, 6.08; N, 8.28.

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EXAMPLE 15

(2S,3S)-3-[2,5-bis(difluoromethoxy)benzyl]amino-2-phenylpiperidine hydrochloride

M.P. 238-239°C.

5 ¹H NMR (free base; CDCl₃) δ 1.64 (m, 3H), 2.04 (m, 1H), 2.76 (m, 2H), 3.18 (m, 1H), 3.28 (d, 1H, J=12), 3.52 (d, 1H, J=12), 3.84 (d, 1H, J=3), 6.12 (t, 1H, J=75), 6.40 (t, 1H, J=75), 6.75 (m, 2H), 6.94 (d, 1H, J=9), 7.24 (m, 5H).

HRMS calc'd for C₂₀H₂₂F₄N₂O₂: 398.1612. Found: 398.1591.

10 EXAMPLE 16

(2S,3S)-3-(5-t-Butyl-2-difluoromethoxybenzyl)amino-2-phenylpiperidine hydrochloride

M.P. 263-264°C (dec).

15 ¹H NMR (free base; CDCl₃) δ 1.24 (s, 9H), 1.42 (m, 1H), 1.62 (m, 1H), 1.80 (m, 1H), 2.10 (m, 1H), 2.80 (m, 2H), 3.24 (m, 2H), 3.58 (d, 1H, J=12), 3.87 (brs, 1H), 6.18 (t, 1H, J=72), 6.86 (d, 1H, J=6), 7.00 (brs, 1H), 7.12 (m, 1H), 7.24 (m, 5H).

HRMS calc'd for C₂₃H₃₀F₂N₂O: 388.2321. Found: 388.2336.

20 EXAMPLE 17

(2S,3S)-3-(2-Isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine hydrochloride

M.P. 245-246°C (dec).

25 ¹H NMR (free base: CDCl₃) δ 1.08 (d, 3H, J=6), 1.12 (d, 3H, J=6), 1.40 (m, 1H), 1.64 (m, 1H), 1.87 (m, 1H), 2.08 (m, 1H), 2.78 (m, 2H), 3.02 (m, 1H), 3.34 (d, 1H, J=15), 3.51 (d, 1H, J=15), 3.85 (d, 1H, J=2), 4.28 (m, 1H), 6.01 (d, 1H, J=9), 6.82 (m, 1H), 6.91 (m, 1H), 7.24 (m, 5H).

HRMS calc'd for C₂₂H₂₇F₃N₂O₂: 408.2024. Found: 408.2019.

30 Anal. calc'd for C₂₂H₂₇F₃N₂O₂•2HCl: C, 54.89; H, 6.07, N, 5.82. Found: C, 54.50; H, 6.24; N, 5.78.

EXAMPLE 18

(2S,3S)-3-(2-Difluoromethoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine hydrochloride

35 M.P. 257-259°C (dec).

1H NMR (free base; CDCl₃) δ 1.44 (m, 1H), 1.58 (m, 1H), 1.78 (m, 1H), 2.03 (m, 1H), 2.78 (m, 2H), 3.20 (m, 1H), 3.32

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(d, 1H, J=15), 3.54 (d, 1H, J=15), 3.87 (d, 1H, J=2), 6.15 (t, 1H, J=72), 6.94 (m, 3H), 7.26 (m, 5H).

HRMS calc'd for $C_{20}H_{21}F_5N_2O_2$: 416.1523. Found: 416.1501.

Anal. calc'd for $C_{20}H_{21}F_5N_2O_2 \cdot 2HCl \cdot 1/3H_2O$: C, 48.50; H, 5 4.81; N, 5.65. Found: C, 48.45; H, 4.57; N, 5.66.

EXAMPLE 19

(2S,3S)-3-(2-Ethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine hydrochloride

M.P. > 275°C (dec).

10 1H NMR (free base; $CDCl_3$) δ 1.13 (t, 3H, J=6), 1.38 (m, 1H), 1.70 (m, 2H), 2.06 (m, 1H), 2.74 (m, 2H), 3.22 (m, 1H), 3.30 (d, 1H, J=15), 3.68 (m, 3H), 3.84 (br s, 1H), 6.55 (d, 1H, J=9), 6.79 (br s, 1H), 6.90 (m, 1H), 7.2 (m, 5H).

HRMS calc'd for $C_{21}H_{25}F_3N_2O_2$: 394.1868. Found: 394.1875.

15 Anal. calc'd for $C_{21}H_{25}F_3N_2O_2 \cdot 2HCl$: C, 53.97; H, 5.82; N, 6.00. Found: C, 53.85; H, 5.79; N, 5.95.

EXAMPLE 20

(2S,3S)-3-(2-Difluoromethoxy-5-nitrobenzyl)amino-2-phenylpiperidine hydrochloride

20 1H NMR (free base; $CDCl_3$) δ 1.50 (m, 1H), 1.66 (m, 1H), 1.98 (m, 2H), 2.82 (m, 2H), 3.28 (m, 1H), 3.42 (d, 1H, J=15), 3.64 (d, 1H, J=15), 3.95 (d, 1H, J=2), 6.30 (t, 1H, J=72), 7.08 (d, 1H, J=8), 7.30 (m, 5H), 8.04 (m, 2H).

FAB HRMS calc'd for $C_{19}H_{21}F_2N_3O_3(M+1)$: 378.1629. Found: 25 378.1597.

EXAMPLE 21

(2S,3S)-3-(2-Difluoromethoxy-5-isopropylbenzyl)amino-2-phenylpiperidine hydrochloride

M.P. 245-247°C (dec).

30 1H NMR (free base; $CDCl_3$) δ 1.19 (2d, 6H, J=7), 1.50 (m, 1H), 1.75 (m, 2H), 2.12 (m, 1H), 2.83 (m, 3H), 3.25 (m, 1H), 3.35 (d, 1H, J=14), 3.60 (d, 1H, J=14), 3.90 (d, 1H, J=3), 6.20 (t, 1H, J=75), 6.90 (m, 2H), 7.00 (m, 1H), 7.30 (m, 5H).

35 HRMS calc'd for $C_{22}H_{28}F_2N_2O$: 374.2170. Found: 374.2207. Anal. calc'd for $C_{22}H_{28}F_2N_2O \cdot 2HCl \cdot 1/3H_2O$: C, 58.28; H, 6.67; N, 6.18. Found: C, 58.17; H, 6.52; N, 6.17.

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EXAMPLE 22

(2S,3S)-3-[5-Acetamido-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine hydrochloride

M.P. > 270°C.

5 ¹H NMR (free base; CDCl₃) δ 1.46 (m, 1H), 1.82 (m, 1H), 2.08 (m, 1H), 2.12 (s, 3H), 2.76 (m, 2H), 3.20 (m, 1H), 3.48 (d, 1H, J=15), 3.58 (d, 1H, J=15), 3.82 (m, 1H), 4.08 (m, 2H), 6.44 (m, 1H), 6.58 (d, 1H, J=10), 6.78 (m, 1H), 7.26 (m, 5H), 7.58 (m, 1H).

10

EXAMPLE 23

(2S,3S)-3-(2-Difluoromethoxy-5-ethylbenzyl)amino-2-phenylpiperidine hydrochloride

M.P. 254-255°C.

15 ¹H NMR (free base; CDCl₃) δ 1.12 (t, 3H, J=10), 1.36 (m, 1H), 1.44 (m, 1H), 1.82 (m, 1H), 2.10 (m, 1H), 2.48 (q, 2H, J=10), 2.8 (m, 1H), 3.10 (m, 1H), 3.34 (d, 1H, J=15), 3.58 (d, 1H, J=15), 3.9 (d, 1H, J=3), 6.12 (t, 1H, J=85), 6.78 (s, 1H), 6.90 (m, 2H), 7.28 (m, 5H).

Anal. calc'd for C₂₁H₂₆F₂N₂O•2HCl: C, 58.19; H, 6.51; N, 6.47. Found: C, 57.90; H, 6.52; N, 6.64.

EXAMPLE 24

cis-3-(5-t-Butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine hydrochloride

A. cis-5-Nitro-6-(trifluoromethoxyphenyl)piperidin-2-

25 one

Under a nitrogen atmosphere, in a round-bottom flask were placed 15 g (79 mmol) of 3-trifluoromethoxybenzaldehyde, 80 mL of ethanol, 11 g (0.26 mol) of ammonium acetate and 12.6 mL (79 mmol) of methyl 4-nitrobutyrate, and 30 the mixture was heated at reflux for 6 hours. After cooling to room temperature, the mixture was concentrated. The remaining material was stirred with ca. 200 mL of CHCl₃ for 30 minutes, filtered and concentrated. The residue purified by flash column chromatography, eluting with 1:49 methanol/chloroform followed by 1:19 methanol/chloroform to obtain 24 g of 5-nitro-6-(3-trifluoromethoxyphenyl)-piperidin-2-one.

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In a round bottom flask were placed 20 g (66 mmol) of the product obtained above, 13 g of KOH and 100 mL of ethanol, and the mixture was stirred at room temperature for 90 minutes. To the system was added ca. 35 mL of 33% sulfuric acid/ethanol. The mixture was poured into 150 mL of water and extracted with three 100 mL portions of CHCl₃. The combined extracts were washed with water, dried (Na₂SO₄) and concentrated. The crude material was purified by column chromatography (300 g of silica gel) using ethyl acetate followed by 1:99 methanol/ethyl acetate as the eluant to obtain 5.8 g of cis-5-nitro-6-(3-trifluoromethoxyphenyl)-piperidin-2-one which contained ca. 12% of the corresponding trans-isomer. This material was purified by a second chromatography to obtain 4.6 g of the cis-product.

15 B. cis-5-Amino-6-(3-trifluoromethoxyphenyl)piperidin-2-one

Under a nitrogen atmosphere, in a three-neck round-bottom flask equipped with a thermometer and a mechanical stirrer, were placed this cis-material and a mixture of THF (200 mL), methanol (50 mL) and water (5 mL). To this stirring solution was added aluminum amalgam (prepared by washing 4.1 g of aluminum foil strips with ether and dipping in 2% aqueous HgCl₂ for 30-45 seconds and washing with ether), and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of diatomaceous earth and the pad washed with THF. The filtrate was concentrated, dissolved in ethyl acetate and treated with 30 mL of ether saturated with HCl. Concentration afforded 3.7 g of crude cis-5-amino-6-(3-trifluoromethoxyphenyl)piperidin-2-one as a waxy solid, m.p. 126-130°C.

30 C. cis-3-(5-t-Butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine hydrochloride

Under a nitrogen atmosphere, in a round-bottom flask were placed 0.38 g (1.4 mmol) of the amine obtained above, 6 mL of acetic acid and 0.32 g (1.66 mmol) of 5-t-butyl-2-methoxybenzaldehyde. The mixture was stirred for 45

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minutes. To the system was added 0.65 g (3.0 mmol) of sodium triacetoxyborohydride in portions, and the mixture was stirred at room temperature overnight. The mixture was concentrated and partitioned between chloroform and H₂O and 5 made basic with 1N aqueous NaOH. The layers were separated and the aqueous phase was extracted with two portions of CHCl₃. The combined organic fractions were washed with H₂O, dried and concentrated. The crude product was purified by flash column chromatography to obtain 0.4 g of cis-5-(5-t-10 butyl-2-methoxybenzyl)amino-6-(3-trifluoromethoxyphenyl)-piperidin-2-one.

Under a nitrogen atmosphere, in a round-bottom flask were placed 0.4 g (0.9 mmol) of the product obtained above and 10 mL of THF. To the system was added 2.2 mL (4.4 mmol) 15 of 2M borane methyl sulfide complex in THF and the mixture was gradually heated and allowed to reflux for 4 hours. The mixture was cooled to room temperature, 2 mL of methanol was added to the system and the mixture was concentrated. To the system was added 5 mL of ethanol and 2.45 of K₂CO₃, and 20 the mixture was heated at reflux for 8 hours and stirred at room temperature overnight. The mixture was concentrated and partitioned between water and CH₂Cl₂. The layers were separated, and the aqueous phase was extracted with three portions of CH₂Cl₂. The combined organic fractions were 25 dried and concentrated to obtain an oil. The oil was dissolved in ethyl acetate, and the solution was treated with ether saturated with HCl. Concentration afforded 70 mg of the title compound as a waxy solid.

M.P. 247°C-249°C.

30 ¹H NMR (free-base, CDCl₃) δ 1.26 (s, 9H), 1.6 (m, 1H), 1.90 (m, 2H), 2.12 (m, 1H), 2.80 (m, 2H), 3.24 (m, 1H), 3.36 (d, 1H, J=15), 3.48 (s, 3H), 3.64 (d, 1H, J=15), 3.86 (m, 1H), 6.60 (d, 1H, J=10), 7.18 (m, 6H).

HRMS Calc'd: C₂₄H₃₁N₂O₂F₃: 436.2330. Found: 436.2326.

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EXAMPLE 25

cis-2-(3,5-Dibromophenyl)-3-(2-methoxy-5-trifluoro-
methoxybenzyl)aminopiperidine

- The title compound was prepared by a procedure similar
 5 to that described in Example 25, with the exception that the
 nitro substituent of the product of the initial reaction [6-
 (3,5-dibromophenyl)-5-nitropiperidin-2-one] was converted to
 an amino group by sequential oxidative cleavage (O_3 , KO^+Bu),
 oxime formation (H_2NOH) and Raney nickel-catalyzed reduction.
 10 The final product can be resolved by treatment with (R)-(-)-
 mandelic acid in isopropanol. Two recrystallizations of the
 solid isolated from this procedure (isopropanol), followed
 by treatment with saturated aqueous sodium bicarbonate
 affords the (2S,3S)-enantiomer; $[\alpha]_D$ (mandelate salt):
 15 +4.11° (MeOH, $c=0.51$).

1H NMR ($CDCl_3$) δ 1.36 (m, 1H), 1.50 (m, 1H), 1.80 (m,
 1H), 2.04 (m, 1H), 2.70 (m, 2H), 3.18 (m, 1H), 3.30 (d, 1H,
 J=18), 3.57 (s, 3H), 3.66 (d, 1H, J=18), 3.75 (m, 1H), 6.63
 (d, 1H, J=9), 6.86 (d, 1H, J=3), 6.97 (dd, 1H, J=6, 9), 7.32
 20 (m, 2H), 7.48 (s, 1H).

EXAMPLE 26

(2S-3S)-3-(2-Difluoromethoxy-5-methylbenzyl)amino-2-
phenylpiperidine hydrochloride

- The title compound was prepared by a procedure similar
 25 to that described in Example 4.

M.P. >275°C.

1H NMR (free-base, $CDCl_3$) δ 1.44 (m, 1H), 1.6 (m, 1H),
 1.84 (m, 1H), 2.10 (m, 1H), 2.20 (s, 3H), 2.80 (m, 2H), 3.22
 (m, 1H), 3.34 (d, 1H, J=15), 3.58 (d, 1H, J=15), 3.90 (d,
 30 1H, J=3), 6.10 (t, 1H, J=72), 6.84 (m, 2H), 7.26 (m, 5H).

HRMS calc'd for $C_{20}H_{24}F_2N_2O$: 347.1929 (M+1). Found:
 347.1911.

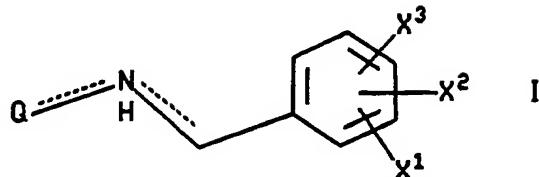
Anal. calc'd for $C_{20}H_{24}F_2N_2O \bullet 2HCl \bullet 0.25H_2O$: C, 56.67; H,
 6.30; N, 6.61. Found: C, 56.81; H, 6.16; N, 6.50.

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CLAIMS

1. A compound of the formula

5



wherein X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl 10 optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from halo, hydrogen, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally 15 substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-

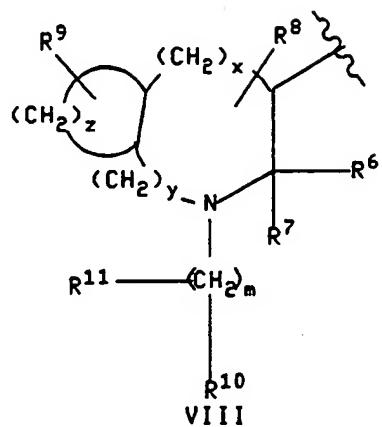
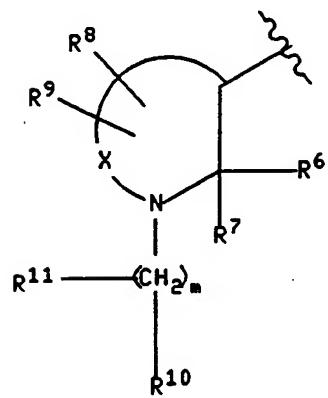
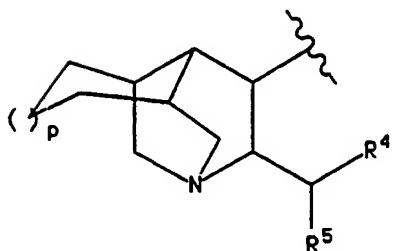
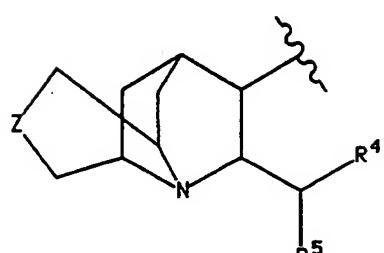
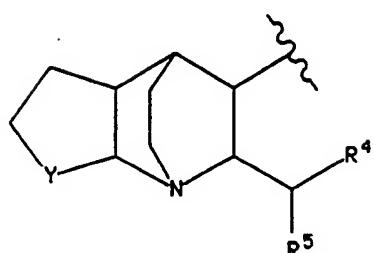
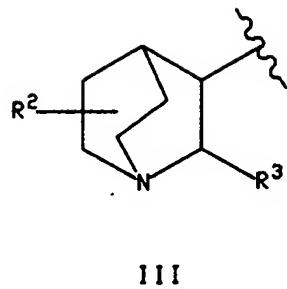
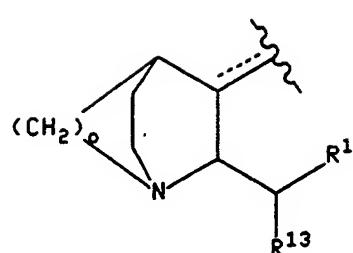
20 alkylamino, di- (C_1-C_6) alkylamino, $\begin{matrix} O \\ || \\ -C-NH-(C_1-C_6)alkyl \end{matrix}$,

25 $\begin{matrix} O \\ || \\ (C_1-C_6)alkyl-C-NH-(C_1-C_6)alkyl \end{matrix}$, hydroxy(C_1-C_4)alkyl, (C_1-

$\begin{matrix} O & O \\ || & || \\ C_4)alkoxy(C_1-C_4)alkyl, -NHCH & -NHC-(C_1-C_6)alkyl; and \end{matrix}$

Q is a group of the formula

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wherein R¹ is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C₁-C₃) alkoxy-carbonyl;

5 R¹³ is selected from (C₃-C₄) branched alkyl, (C₅-C₆) branched alkenyl, (C₅-C₇) cycloalkyl, and the radicals named

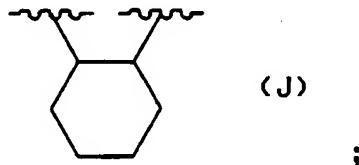
10 in the definition of R¹;

R² is hydrogen or (C₁-C₆) alkyl;

R³ is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R³ may optionally be substituted with from one to three substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms;

15 Y is (CH₂)₁ wherein l is an integer from one to three, or Y is a group of the formula

20



25 Z is oxygen, sulfur, amino, (C₁-C₃)alkylamino or (CH₂)_n, wherein n is zero, one or two;

o is two or three;

p is zero or one;

R⁴ is furyl, thienyl, pyridyl, indolyl, biphenyl, or
30 phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, (C₁-C₃) alkoxy-carbonyl and
35 benzyloxycarbonyl;

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R⁵ is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms;

each of the two dashed lines in formula I and the dashed line in formula II represent an optional double bond that may optionally exist when Q is a group of the formula II;

X is (CH₂)_q wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said (CH₂)_q may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said (CH₂)_q may optionally be substituted with R⁸, and wherein any one of the carbon atoms of said (CH₂)_q may optionally be substituted with R⁹;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of (CH₂)_m may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said (CH₂)_m may optionally be substituted with R¹¹;

R⁶ is a radical selected from hydrogen, (C₁-C₆) straight or branched alkyl, (C₃-C₇) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C₂-C₆) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C₂-C₆) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C₁-C₆) alkyl, (C₁-C₆) alkoxy-(C₁-C₆) alkyl,

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||

R¹⁰ is NHCR¹², NHCH₂R¹², NHSO₂R¹² or one of the radicals set forth in any of the definitions of R⁶, R⁸ and R⁹;

5 R¹¹ is oximino (=NOH) or one of the radicals set forth in any of the definitions of R⁶, R⁸ and R⁹; and

R¹² is (C₁-C₆)alkyl, hydrogen, phenyl(C₁-C₆)alkyl or phenyl optionally substituted with (C₁-C₆)alkyl;

with the proviso that (a) when m is 0, R¹¹ is absent,
10 (b) neither R⁸, R⁹, R¹⁰ nor R¹¹ can form, together with the carbon to which it is attached, a ring with R⁷, (c) when Q is a group of the formula VIII, R⁸ and R⁹ cannot be attached to the same carbon atom, (d) when R⁸ and R⁹ are attached to the same carbon atom, then either each of R⁸ and R⁹ is
15 independently selected from hydrogen, fluoro, (C₁-C₆) alkyl, hydroxy-(C₁-C₆)alkyl and (C₁-C₆)alkoxy-(C₁-C₆)alkyl, or R⁸ and R⁹, together with the carbon to which they are attached, form a (C₃-C₆) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are
20 attached, (e) the nitrogen of formula I can not be double bonded to both Q and the substituted benzyl group to which it is attached, (f) when Q is a group of the formula VII and q is 2 and either R⁸ or R⁹ is 5-hydroxy-(C₁-C₆)alkyl or 5-(C₁-C₆)alkoxy-(C₁-C₆)alkyl, then the other of R⁸ and R⁹ is either
25 5-(C₁-C₆)alkyl or hydrogen; (g) when Q is a group of the formula VII and q is 2, then neither R⁸ nor R⁹ is 4-hydroxy-(C₁-C₆)alkyl or 4-(C₁-C₆)alkoxy-(C₁-C₆)alkyl, and (h) when neither X¹, X² nor X³ is a fluorinated alkoxy group, at least one of R¹, R³, R⁴, R⁵, R⁶, R⁷ and R¹³ is an aryl group
30 substituted with a fluorinated alkoxy group;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein Q is a group of the formula II wherein o is two or three and each of R¹ and R¹³ is phenyl or substituted phenyl.

35 3. A compound according to claim 1 wherein Q is a group of the formula III, R² is hydrogen and R³ is phenyl or substituted phenyl.

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4. A compound according to claim 1 wherein Q is a group of the formula IV wherein l is one or two and each of R⁴ and R⁵ is phenyl or substituted phenyl.
5. A compound according to claim 1 wherein Q is a group of the formula V wherein n is zero or one and each of R⁴ and R⁵ is phenyl or substituted phenyl.
6. A compound according to claim 1 wherein Q is a group of the formula VI wherein p is one and each of R⁴ and R⁵ are phenyl or substituted phenyl.
- 10 7. A compound according to claim 1 wherein Q is a group of the formula VII wherein q is two, three or four, m is zero and R⁶ is phenyl or substituted phenyl.
- 15 8. A compound according to claim 1 wherein Q is a group of the formula VIII wherein y is zero, x is zero or one, z is three or four, m is zero and R⁶ is phenyl or substituted phenyl.
9. A compound according to claim 1, wherein said compound is 2-(diphenylmethyl)-N-((2-difluoromethoxy)-phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine.
- 20 10. A compound according to claim 1, wherein said compound is (2S,3S)-N-(2-methoxy-5-trifluoromethoxy-phenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-amine.
11. A compound according to claim 1, wherein said compound is (2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxy)-benzyl]aminopiperidine.
- 25 12. A compound according to claim 1, wherein said compound is (2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine.
- 30 13. A compound according to claim 1, wherein said compound is (2S,3S)-3-(2-hydroxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine.
- 35 14. A compound according to claim 1, wherein said compound is (2S,3S)-2-phenyl-3-(3-trifluoromethoxybenzyl)-aminopiperidine.

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15. A compound according to claim 1, wherein said compound is (2S,3S)-1-(5,6-dimethoxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine.

16. A compound according to claim 1, wherein said 5 compound is (2S,3S)-2-phenyl-3-(2-trifluoromethoxybenzyl)-aminopiperidine.

17. A compound according to claim 1, wherein said compound is (2S,3S)-3-[5-chloro-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine.

10 18. A compound according to claim 1, wherein said compound is (2S,3S)-3-(5-t-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine.

19. A compound according to claim 1, wherein said compound is 3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-15 trifluoromethoxyphenyl)piperidine.

20. A compound according to claim 1, wherein said compound is 3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine.

21. A compound according to claim 1, wherein said 20 compound is 3-(2-difluoromethoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine.

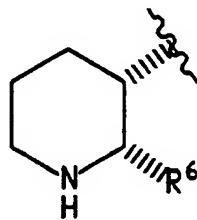
22. A compound according to claim 1, wherein X¹ is 5-trifluoromethoxy, X² is hydrogen and X³ is 2-methoxy.

23. A compound according to claim 1 wherein X¹ is 2-25 trifluoromethoxy and each of X² and X³ is hydrogen.

24. A compound according to claim 1, wherein X¹ is 2-(2,2,2-trifluoroethoxy) and each of X² and X³ is hydrogen.

25. A compound according to claim 1 wherein Q is a group of the formula

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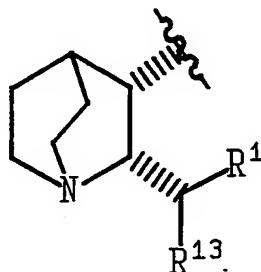
wherein X¹ is 2-trifluoromethoxy, 2-methoxy or 2-(2,2,2-trifluoroethoxy), X² is 5-halo, 5-(C₁-C₆) alkyl, or 5-(C₁-C₆

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alkoxy optionally substituted with from one to three fluorine atoms, and R⁶ is substituted or unsubstituted phenyl.

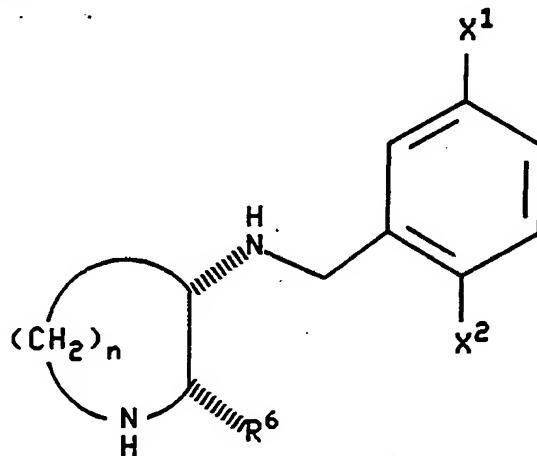
26. A compound according to claim 1 wherein Q is a
5 group of the formula

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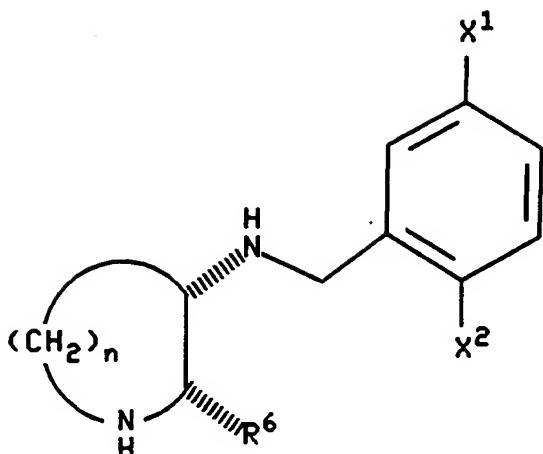


30 wherein n is an integer from 2 to 4, X¹ is hydrogen or (C₁-C₄)alkyl, X² is OCF₃ or OCHF₂, and R⁶ is phenyl optionally substituted with a substituent selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluorine and chlorine.

28. A compound according to claim 1 having the formula

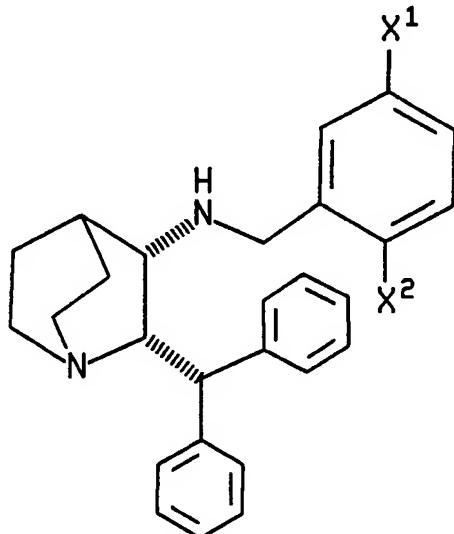
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wherein n is an integer from 2 to 4, X¹ is OCF₃ or OCHF₂, X² is (C₁-C₄)alkoxy, and R⁶ is phenyl optionally substituted with a substituent selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, 15 fluorine and chlorine.

29. A compound according to claim 1 having the formula

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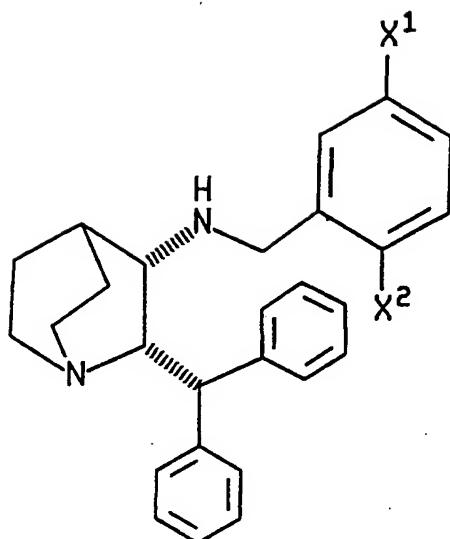
30 wherein X¹ is (C₁-C₄)alkyl or hydrogen, X² is OCF₃ or OCHF₂, and one or both of the phenyl moieties of the benzhydryl group may be optionally substituted with a substituent selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluorine and chlorine.

35 30. A compound according to claim 1 having the formula

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wherein X¹ is OCF₃ or OCHF₂, X² is (C₁-C₄)alkoxy, and one or
15 both of the phenyl moieties of the benzhydryl group may be
optionally substituted with a substituent selected from (C₁-
C₄)alkyl, (C₁-C₄)alkoxy, fluorine and chlorine.

31. A compound according to claim 1, wherein X¹ is a 2-(C₁-C₄)alkoxy group, X² is hydrogen and X³ is a 5-OCF₃ or 5-OCHF₂ group.

32. A compound according to claim 1, wherein X¹ is a 2-OCF₃ or 2-OCHF₂ group, X² is hydrogen and X³ is (C₁-C₄)alkyl.

33. A compound according to claim 1, wherein each of R¹, R³, R⁴, R⁶ and R¹³, if present, is selected from phenyl
25 optionally substituted with (C₁-C₄) alkyl, (C₁-C₄) alkoxy,
fluorine, chlorine or trifluoromethoxy, each of R², R⁷, R⁸, R⁹
and R¹⁰, if present, is hydrogen, and m is zero if Q is a
group of the formula VII or VIII.

34. A pharmaceutical composition for treating or
30 preventing a condition selected from the group consisting of
inflammatory diseases, anxiety, colitis, depression or
dysthymic disorders, psychosis, pain, gastroesophageal
reflux disease, allergies, chronic obstructive airways
disease, hypersensitivity disorders, vasospastic diseases,
35 fibrosing and collagen diseases, reflex sympathetic
dystrophy, addiction disorders, stress related somatic
disorders, peripheral neuropathy, neuralgia,

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neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising an amount of a compound according to claim 1 effective in preventing or treating such condition 5 and a pharmaceutically acceptable carrier.

35. A method of treating or preventing a condition selected from the group consisting of inflammatory diseases anxiety, colitis, depression or dysthymic disorders, psychosis, pain, gastroesophageal reflux disease, allergies, 10 chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to 15 immune enhancement or suppression and rheumatic diseases in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in preventing or treating such condition.

20 36. A pharmaceutical composition for antagonizing the effects of substance P in a mammal, comprising a substance P antagonizing effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

37. A method of antagonizing the effects of substance 25 P in a mammal, comprising administering to said mammal a substance P antagonizing effective amount of a compound according to claim 1.

38. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or 30 prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

35 39. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated

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neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

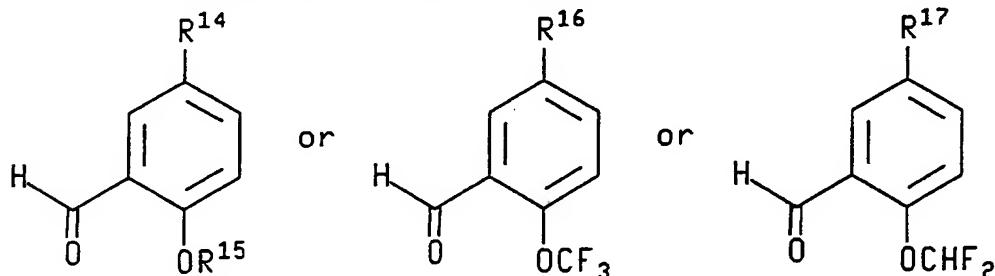
40. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition and a pharmaceutically acceptable carrier.

41. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in treating or preventing such condition.

42. A radioactive isotope of a compound according to claim 1.

43. A radioactive isotope as claimed in claim 42, wherein said radioactive isotope is a tritium or ¹⁴C-isotope of said compound.

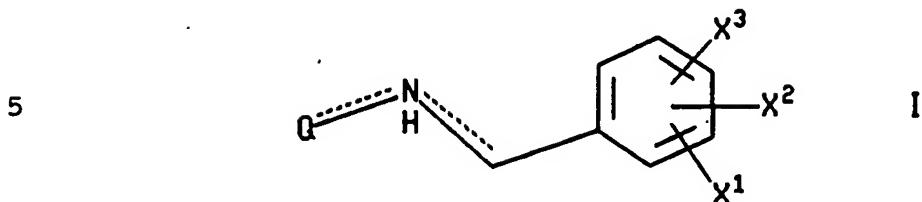
44. A compound of the formula



wherein R¹⁴ trifluoromethoxy or difluoromethoxy, R¹⁵ is (C₁-C₄)alkyl, R¹⁶ is difluoromethoxy or (C₁-C₄)alkyl and R¹⁷ is trifluoromethoxy, difluoromethoxy, (C₁-C₄)alkyl or (C₁-C₄)alkoxy.

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45. A process for preparing a compound having the formula



wherein X¹ is hydrogen, (C₁-C₁₀) alkoxy optionally substituted
10 with from one to three fluorine atoms or (C₁-C₁₀) alkyl
optionally substituted with from one to three fluorine
atoms;

X^2 and X^3 are independently selected from halo, hydrogen, nitro, (C_1-C_{10}) alkyl optionally substituted with 15 from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-

20 alkylamino, di-(C₁-C₆)alkylamino, -C(=O)-NH-(C₁-C₆)alkyl,

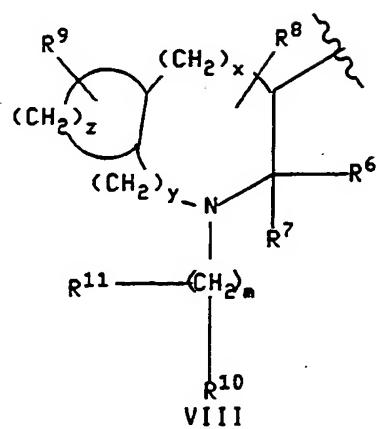
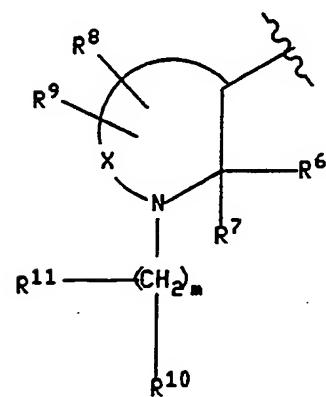
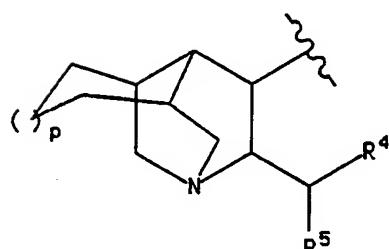
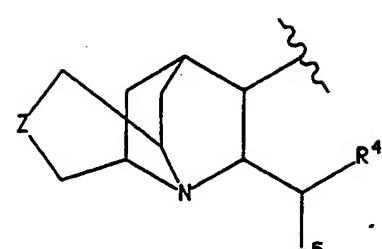
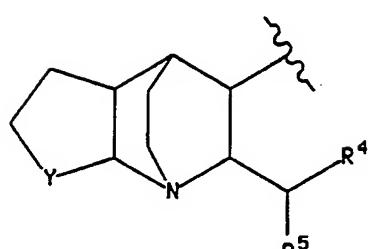
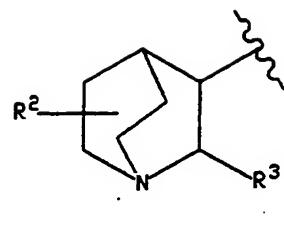
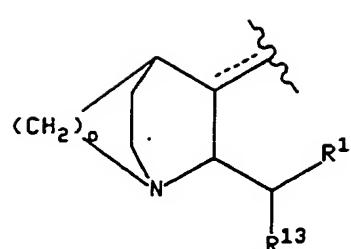
C_1) alkoxy ($\text{C}_1\text{-C}_4$) alkyl, $-\text{NHCH}=\text{O}$ and $-\text{NHC}(=\text{O})-(\text{C}_1\text{-C}_6)$ alkyl; and

30 Q is a group of the formula

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wherein R¹ is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C₁-C₃) alkoxy-carbonyl;

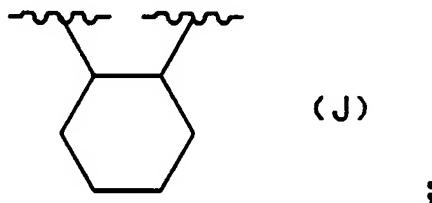
R¹³ is selected from (C₃-C₄) branched alkyl, (C₅-C₆) branched alkenyl, (C₅-C₇) cycloalkyl, and the radicals named in the definition of R¹;

R² is hydrogen or (C₁-C₆) alkyl;

R³ is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R³ may optionally be substituted with from one to three substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms;

Y is (CH₂)_l, wherein l is an integer from one to three, or Y is a group of the formula

20



25

Z is oxygen, sulfur, amino, (C₁-C₃)alkylamino or (CH₂)_n, wherein n is zero, one or two;

o is two or three;

p is zero or one;

30 R⁴ is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, (C₁-C₃) alkoxy-carbonyl and benzyloxycarbonyl;

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R⁵ is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms;

each of the two dashed lines in formula I and the dashed line in formula II represent an optional double bond that may optionally exist when Q is a group of the formula II;

X is (CH₂)_q wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said (CH₂)_q may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said (CH₂)_q may optionally be substituted with R⁸, and wherein any one of the carbon atoms of said (CH₂)_q may optionally be substituted with R⁹;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of (CH₂)_m may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said (CH₂)_m may optionally be substituted with R¹¹;

R⁶ is a radical selected from hydrogen, (C₁-C₆) straight or branched alkyl, (C₃-C₇) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C₂-C₆) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C₂-C₆) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C₁-C₁₀) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₁₀) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C₁-C₆) alkyl, (C₁-C₆) alkoxy-(C₁-C₆) alkyl,

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- O O
- (C₁-C₆)-alkylamino, (C₁-C₆)alkyl-O-C-, (C₁-C₆) alkyl-O-C-
- O O
- (C₁-C₆) alkyl, (C₁-C₆)alkyl-C-O-, (C₁-C₆)alkyl-C-
- O O
- (C₁-C₆) alkyl-O-, (C₁-C₆)alkyl-C-, (C₁-C₆)alkyl-C-
- O
- (C₁-C₆) alkyl-, di-(C₁-C₆)alkylamino, -CNH-(C₁-C₆) alkyl, (C₁-C₆)-
- O O O
- alkyl-C-NH-(C₁-C₆)alkyl, -NHCH and -NHC-(C₁-C₆) alkyl; and
wherein one of the phenyl moieties of said benzhydryl may
optionally be replaced by naphthyl, thienyl, furyl or
pyridyl;
- R⁷ is hydrogen, phenyl or (C₁-C₆)alkyl;
or R⁶ and R⁷, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to
7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;
- R⁸ and R⁹ are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, hydroxy-(C₁-C₆)-alkyl, (C₁-C₆)alkoxy-(C₁-C₆)alkyl, (C₁-C₆)alkylamino,
di-(C₁-C₆)alkylamino, (C₁-C₆)alkoxy,
- O O
- (C₁-C₆)alkyl-O-C-, (C₁-C₆)alkyl-O-C-(C₁-C₆)alkyl,
- O O
- (C₁-C₆)alkyl-C-O-, (C₁-C₆)alkyl-C-(C₁-C₆)alkyl-O-,
- O O
- (C₁-C₆)alkyl-C-, (C₁-C₆)alkyl-C-(C₁-C₆)alkyl-, and the radicals set forth in the definition of R⁶;

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$\overset{\text{||}}{\text{R}^{10}}$ is NHCR^{12} , $\text{NHCH}_2\text{R}^{12}$, $\text{NHSO}_2\text{R}^{12}$ or one of the radicals set forth in any of the definitions of R^6 , R^8 and R^9 ;

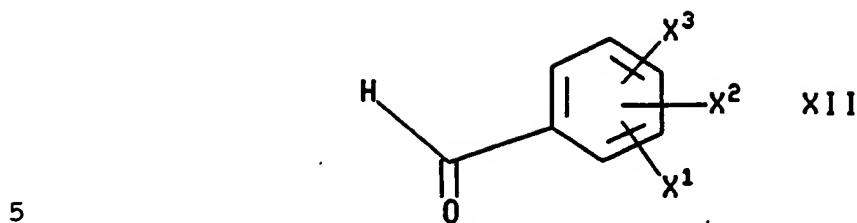
5 R^{11} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^6 , R^8 and R^9 ;

10 R^{12} is $(\text{C}_1\text{-C}_6)$ alkyl, hydrogen, phenyl $(\text{C}_1\text{-C}_6)$ alkyl or phenyl optionally substituted with $(\text{C}_1\text{-C}_6)$ alkyl; and

15 with the proviso that (a) when m is 0, R^{11} is absent, (b) neither R^8 , R^9 , R^{10} nor R^{11} can form, together with the carbon to which it is attached, a ring with R^7 , (c) when Q is a group of the formula VIII, R^8 and R^9 cannot be attached to the same carbon atom, (d) when R^8 and R^9 are attached to the same carbon atom, then either each of R^8 and R^9 is independently selected from hydrogen, fluoro, $(\text{C}_1\text{-C}_6)$ alkyl, hydroxy- $(\text{C}_1\text{-C}_6)$ alkyl or $(\text{C}_1\text{-C}_6)$ alkoxy- $(\text{C}_1\text{-C}_6)$ alkyl, or R^8 and R^9 , together with the carbon to which they are attached, form a $(\text{C}_3\text{-C}_6)$ saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached, (e) the nitrogen of formula I can not be double bonded to both Q and the substituted benzyl group to which it is attached, (f) when Q is a group of the formula VII and q is 2 and either R^8 or R^9 is 5-hydroxy- $(\text{C}_1\text{-C}_6)$ alkyl or 5-($\text{C}_1\text{-C}_6$)alkoxy- $(\text{C}_1\text{-C}_6)$ alkyl, then the other of R^8 and R^9 is either 5-($\text{C}_1\text{-C}_6$)alkyl or hydrogen; (g) when Q is a group of the formula VII and q is 2, then neither R^8 nor R^9 is 4-hydroxy- $(\text{C}_1\text{-C}_6)$ alkyl or 4-($\text{C}_1\text{-C}_6$)alkoxy- $(\text{C}_1\text{-C}_6)$ alkyl, and (h) when neither X^1 , X^2 nor X^3 is a fluorinated alkoxy group, at least one of R^1 , R^3 , R^4 , R^5 , R^6 , R^7 and R^{13} is an aryl group 20 substituted with a fluorinated alkoxy group; or a pharmaceutically acceptable salt thereof;

25 comprising reacting a compound of the formula Q-NH_2 , wherein Q is defined as above, with a compound of the formula

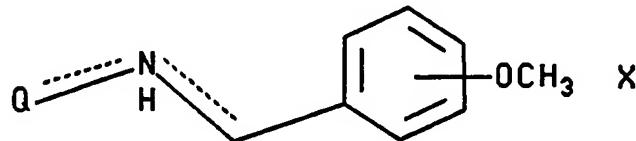
-75-



wherein X^1 , X^2 and X^3 are defined as above, in the presence of a reducing agent.

46. A process according to claim 45, wherein said compound of the formula $Q-NH_2$ is obtained by subjecting a compound of the formula

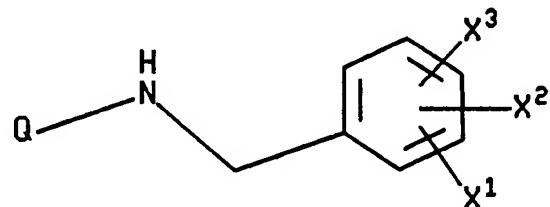
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wherein Q is defined as in claim 45, to hydrolytic removal of the methoxybenzyl group.

20 47. A process for preparing a compound of the formula

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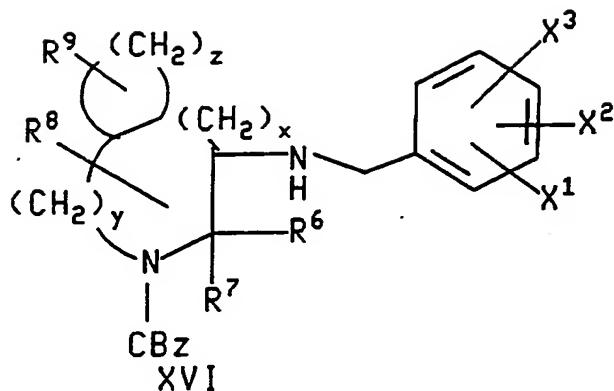
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wherein Q is a group of the formula VIII, as defined in claim 45, and wherein X^1 , X^2 and X^3 are defined as in claim 45 and m is zero, comprising reacting a compound of the formula

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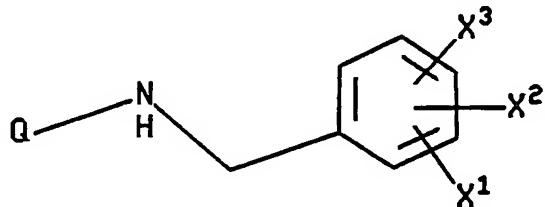
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wherein X^1 , X^2 , X^3 , R^6 , R^7 , R^8 , R^9 , x , y and z are defined as in claim 45, with ammonium formate in the presence of palladium on charcoal.

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48. A process for preparing a compound of the formula

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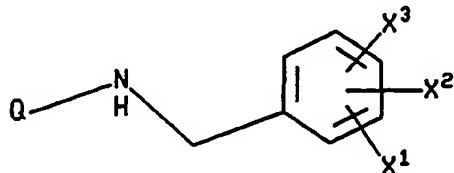
wherein Q is a group of the formula VII or VIII, as defined in claim 45, and m is an integer other than zero, comprising reacting the corresponding compound wherein m is equal to

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zero with a compound of the formula $R^{11}-(CH_2)_m-L'$ wherein L' is halo, mesylate or tosylate, R^{10} , R^{11} and m are defined as in claim 45, and one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond, and wherein one of the carbons of said $(CH_2)_m$ may optionally be substituted with R^{11} .

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49. A process for preparing a compound of the formula

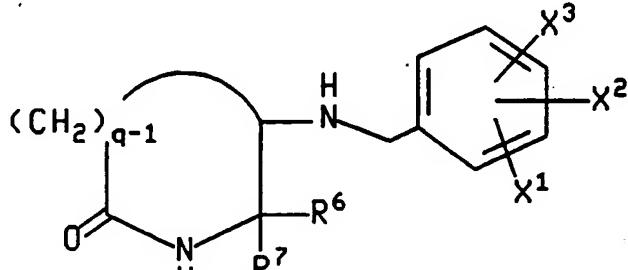


-77-

wherein Q is a group of the formula VII, as defined in claim 45, and wherein X¹, X², and X³ are defined as in claim 45, comprising reacting a compound of the formula

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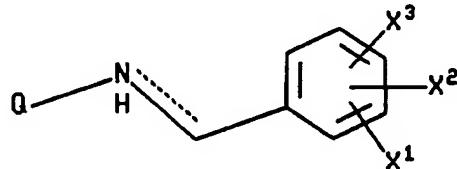


XIV

wherein X¹, X², X³, R⁶, R⁷ and q are defined as in claim 45, with a reducing agent.

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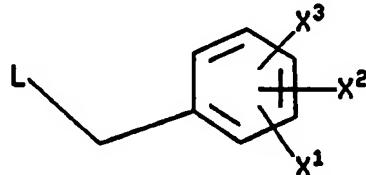
50. A process for preparing a compound of the formula



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wherein Q, X¹, X² and X³ are defined as in claim 45, comprising reacting a compound of the formula Q-NH₂, wherein Q is defined as in claim 45, with a compound of the formula

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wherein L is a leaving group.

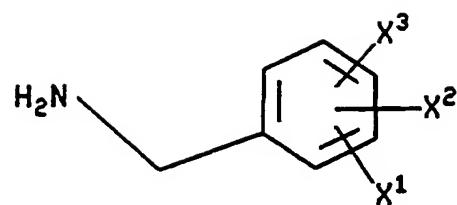
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51. A process for preparing a compound of the formula I, as defined in claim 45, wherein Q is a group of the formula II and there exists a double bond between Q and the adjacent nitrogen, comprising reacting a compound of the formula Q=O, wherein Q is defined as above, with the appropriate benzylamine of the formula

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wherein X^1 , X^2 and X^3 are defined as in claim 45.

52. A compound according to claim 1, wherein said compound is a substance P receptor antagonist.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 92/03571

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 C07D205/02;	A61K31/395;	C07D453/02;	C07D211/08
C07D207/02;	C07D209/00;	C07D209/56;	C07D211/00

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols	
Int.C1. 5	C07D ;	A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
P,X	WO,A,9 118 899 (PFIZER) 12 December 1991 see the whole document ---	1-52
X	WO,A,9 005 525 (PFIZER) 31 May 1990 see the whole document ---	1-52
X	WO,A,9 005 729 (PFIZER) 31 May 1990 see the whole document ---	1-52
P,X	WO,A,9 201 688 (PFIZER) 6 February 1992 see the whole document --- -/-	1-52

⁶ Special categories of cited documents :¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

⁷ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention⁸ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step⁹ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art¹⁰ document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

1

06 OCTOBER 1992

Date of Mailing of this International Search Report

23.11.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

GETTINS M.P.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	<p>CHEMICAL ABSTRACTS, vol. 114, no. 15, 15 April 1991, Columbus, Ohio, US; abstract no. 136489W, MCLEAN ET AL: 'Activity and distribution of binding sites in brain of a nonpeptide substance p (NK1) receptor antagonist' page 122 ; column 1 ; see abstract</p> <p>---</p>	1-52
P,X	<p>CHEMICAL ABSTRACTS, vol. 115, no. 11, 16 September 1991, Columbus, Ohio, US; abstract no. 106745E, ROUSSINI ET AL: 'Selectivity and specificity of new non-peptide, quinuclidine antagonists of substance P.' page 148 ; column 1 ; see abstract</p> <p>---</p>	1-52
P,X	<p>CHEMICAL ABSTRACTS, vol. 115, no. 7, 19 September 1991, Columbus, Ohio, US; abstract no. 71348Y, LOWE ET AL: 'Preparation and radiolabelling of Cp-96,343, the first non-peptide substance P- antagonist.' page 770 ; column 1 ; see abstract</p> <p>---</p>	1-52
A	<p>US,A,3 560 510 (WARAWA) 2 February 1971 see the whole document</p> <p>---</p>	1-33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/03571

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Given the extremely large number of compounds resulting from formula I the search has been restricted to the compounds sufficiently supported by the description (Examples & I where Q=III or VII)
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9203571
SA 60286

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 06/10/92

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9118899	12-12-91	AU-A-	7860291	31-12-91
-----	-----	CA-A-	2003441	23-05-90
WO-A-9005525	31-05-90	EP-A-	0409931	30-01-91
		WO-A-	9005729	31-05-90
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WO-A-9005729	31-05-90	WO-A-	9005525	31-05-90
		CA-A-	2003441	23-05-90
		EP-A-	0409931	30-01-91
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WO-A-9201688	06-02-92	AU-A-	7894891	18-02-92
-----	-----	-----	-----	-----
US-A-3560510	02-02-71	None		-----
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